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ORIGINAL ARTICLE

Association of unit-wide oxygen saturation target on incidence of pulmonary hypertension in very low birthweight premature infants

U Kanaan[1,2,3], B Srivatsa[3,4], J Huckaby[2] and M Kelleman[1]

OBJECTIVE: Assess the effect of increasing pulse oximetry targets on incidence of pulmonary hypertension in very low birthweight premature infants.

STUDY DESIGN: Retrospective cohort study comparing pulmonary hypertension incidence among three cohorts of premature infants exposed to varying oxygen saturation targets (Cohort 1: $n = 459$, 1 May 2009 to 30 April 2011, 85–94%; Cohort 2: $n = 474$, 1 May 2011 to 31 May 2013, 88–94%; Cohort 3: $n = 387$, 1 June 2013 to 31 May 2015, 90–95%). Subjects had birth weight < 1500 g and gestational age 23–32 weeks. Chi-square, Kruskall–Wallis and Anderson–Darling tests were used, as well as multivariable logistic regression.

RESULTS: Incidence of pulmonary hypertension declined with higher oxygen saturation targets (19.0% Cohort 1, 7.9% Cohort 2, 9.6% Cohort 3, $P < 0.001$). Other parameters were largely not different between cohorts though rates of chorioamnionitis and prenatal steroids increased and oxygen use, inhaled nitric oxide use, necrotizing enterocolitis and patent ductus arteriosus ligation decreased over time.

CONCLUSION: Higher oxygen saturation targets for very low-birthweight premature infants were associated with reduced rates of pulmonary hypertension in this retrospective cohort study.

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INTRODUCTION

Pulmonary hypertension (PH) is an increasingly recognized cause of morbidity and mortality in premature infants.[1–5] Both hypoxia and hyperoxia have been implicated as potential contributors to PH pathogenesis in infancy.[6–12] Optimal oxygen saturation (SpO_2) to reduce the risk for developing PH in premature infants has not been identified.

Indeed, the larger question of optimal oxygen SpO_2 for premature infants more generally remains an area of active inquiry and debate.[13–16] Concern for the potential of worsening retinopathy of prematurity (ROP) from excessive oxygen exposure has led to reduced SpO_2 targets;[17–19] however other research suggests SpO_2 target may not significantly impact development[20] or progression of ROP.[21] In addition to the controversy over ROP, other morbidities such as patent ductus arteriosus (PDA)[22] and necrotizing enterocolitis (NEC)[14] may also be affected by SpO_2 targets. Perhaps the most important and definitive endpoint, mortality, appears to also be affected by SpO_2 targets and, while not all studies are consistent, the weight of evidence suggests that higher SpO_2 targets are associated with lower risk of mortality.[13,14,17,23]

One possible mechanism to explain the observed reduction in mortality in babies with higher SpO_2 targets is that they might have lower rates of PH. Unfortunately, PH diagnosis was not reported in the large saturation targeting trials[14,18,23] and was an exclusion criterion in one.[20] Hypoxia is a known contributor to the development of PH via various mechanisms[6,24–27] and infants with BPD have been shown to have a more robust pulmonary vasoconstrictive response to hypoxia than controls.[7] PH has been shown to be an independent risk factor for mortality in BPD even when controlling for BPD disease severity.[1,4,5] We, therefore, hypothesized that increased SpO_2 targets would lead to a reduction in PH in very low birthweight premature infants.

To investigate this hypothesis, we studied the rate of PH diagnosis in a large population of at risk premature infants exposed to different SpO_2 target ranges. On the basis of the results of several large oxygen saturation targeting trials, the neonatal intensive care unit (NICU) at Northside Hospital in Atlanta, Georgia, a large, community-based level III NICU, has twice increased its SpO_2 targets over the last 5 years. We set out to investigate whether rates of PH diagnosis and PH medication use changed with increasing SpO_2 targets.

METHODS

This is a retrospective cohort study comparing three sets of patients from eras defined by the unit-wide SpO_2 targets. A total of 1340 premature infants with gestational age between 23 and 32 weeks, inclusive, and birth weight < 1500 gm admitted to Northside Hospital NICU in Atlanta Georgia between May 1 2009 and May 31 2015 were studied. Cohort 1 consisted of 459 patients born between May 1 2009 and April 30 2011. The unit-wide SpO_2 target range during that time frame was 85–94%. Cohort 2 was comprised of 494 patients born between May 1 2011 and May 31 2013 with SpO_2 target range of 88–94%. Cohort 3 included 387 patients born between June 1 2013 and May 31 2015 with SpO_2 target range of 90–95%. The bedside SpO_2 alarm limits were identical to the targeted SpO_2 ranges for the study duration, giving real-time feedback to bedside caregivers.

[1]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA; [2]Children's Healthcare of Atlanta, Atlanta, GA, USA; [3]Northside Hospital, Atlanta, GA, USA and [4]Mednax, Sunrise, FL, USA. Correspondence: Dr U Kanaan, Pediatrics, Emory University Sibley Heart Center Cardiology, The McGill Building, Suite 400 2835 Brandywine Rd, Atlanta 30341, GA, USA.
E-mail: kanaanu@kidsheart.com
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Table 1. Patient characteristics

	Cohort 1, N = *459*	*Cohort 2*, N = *494*	*Cohort 3, N = 387*	P-*value*[a]
Prenatal characteristics				
Maternal pregnancy induced hypertension	145 (31.6%)	146 (29.6%)	128 (33.1%)	0.526
Maternal chorioamnionitis	20 (4.4%)	47 (9.5%)	39 (10.1%)	0.002
Prenatal steroids	392 (85.4%)	442 (89.5%)	351 (90.7%)	0.037
Multiple gestation	150 (32.7%)	152 (30.8%)	111 (28.7%)	0.455
Neonatal characteristics				
Gestational age at birth, weeks	28 (26–30)	28 (26–30)	28 (26–30)	0.767
Small for gestational age	111 (24.2%)	108 (21.9%)	83 (21.4%)	0.578
Birthweight, grams	1000 (765–1258)	1023 (782–1268)	1044 (775–1290)	0.265
Mother of Hispanic origin	45 (9.8%)	43 (8.7%)	49 (12.7%)	0.147
Race of mother				
Black	180 (39.2%)	217 (43.9%)	167 (43.2%)	0.007
White	207 (45.1%)	195 (39.5%)	139 (35.9%)	
Asian	14 (3.1%)	31 (6.3%)	32 (8.3%)	
Missing or unknown	58 (12.6%)	51 (10.3%)	49 (12.7%)	
Gender				
Male	236 (51.4%)	250 (50.6%)	197 (50.9%)	0.969
Female	223 (48.6%)	244 (49.4%)	190 (49.1%)	
Surfactant in delivery room	153 (33.3%)	181 (36.6%)	138 (35.7%)	0.553
Apgar score at 5 min				
<3	29 (6.3%)	20 (4.1%)	18 (4.7%)	0.257
>3	428 (93.7%)	471 (95.9%)	369 (95.3%)	
Respiratory characteristics				
Oxygen on day of life 28	250 (65.3%)	251 (60.3%)	189 (57.3%)	0.084
Oxygen at 36 weeks CGA	120 (34.2%)	81 (21.8%)	72 (24.9%)	<0.001
Use of inhaled nitric oxide	29 (6.5%)	15 (3.1%)	10 (2.6%)	0.007
Steroids for CLD	46 (10.2%)	109 (22.3%)	79 (20.7%)	<0.001
Comorbidity characteristics				
PDA ligation	36 (8.0%)	17 (3.5%)	8 (2.1%)	<0.001
Necrotizing enterocolitis	40 (8.9%)	20 (4.1%)	9 (2.4%)	<0.001
Presence of ROP at discharge				
None/Mild ($<$ stage 2)	353 (93.9%)	389 (96.0%)	303 (93.8%)	0.293
Severe ($>$ stage 2)	23 (6.1%)	16 (4.0%)	20 (6.2%)	
IVH grade				
None/Mild (<2)	392 (91.2%)	428 (92.2%)	335 (92.5%)	0.747
Severe (>2)	38 (8.8%)	36 (7.8%)	27 (7.5%)	
Invasive infection after day of life 3	31 (7.2%)	28 (6.0%)	22 (6.0%)	0.721

Abbreviations: CGA, corrected gestational age; CLD, chronic lung disease; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity. [a]Overall comparison across Cohort 1, 2 & 3; categorical variables compared using Chi-square test; continuous variables compared using Kruskal–Wallis test.

Also, as part of a quality assurance initiative, data from a computerized system tracking pulse oximetry ranges over longer stretches of time provided feedback starting in 2011.

Institutional review board approval was obtained from all participating institutions: Northside Hospital, Pediatrix Medical Group and Children's Healthcare of Atlanta.

Clinical demographics

Antenatal, birth and neonatal characteristics were obtained from the Vermont-Oxford Network database, as well as the clinical and administrative records maintained by neonatology group staffing the NICU (Babysteps, Pediatrix Medical Group). An emphasis was placed on investigating parameters believed to be associated with PH diagnosis such as small for gestational age (SGA, defined as birthweight $<$ 10th percentile for gestational age[28]), maternal chorioamnionitis and patent ductus arteriosus (PDA).

Outcomes

The standard practice in the Northside Hospital NICU is to perform monthly echocardiograms to assess for PH in premature infants requiring respiratory support. A consistent group of cardiologists interpreted echocardiograms during the timeframe of the study and all had received instruction from the Pulmonary Hypertension Program Director (Kanaan) on standard PH assessment and diagnostic criteria. Criteria for consideration of a PH diagnosis were standardized (including elevated tricuspid regurgitant velocity (>3 m s^{-1}, >36 mm Hg), elevated pulmonary insufficiency end-diastolic velocity (>1.5 m s^{-1}, >9 mm Hg), right to left atrial shunting, right to left ventricular shunting, right to left ductal shunting, right ventricular dilation, right ventricular hypertrophy, right ventricular dysfunction); however clinical judgment to account for other factors impacting cardiovascular physiology was stressed leaving the ultimate PH diagnosis at treating physicians' discretion. Many subjects had more than one echocardiogram and diagnosis of PH on any study led to assignment to the PH group for the purposes of this study (even if PH had not been present on prior studies or resolved in follow up). The diagnosis of PH was made by the treating neonatologist and pediatric cardiologist based on supporting imaging and clinical data, with the neonatologist placing the diagnosis in the medical record. Use of medications to treat PH was at the treating physicians' discretion. Documentation of medication use was obtained from the medical record and confirmed with the NICU pharmacy. PH-specific medication use, mortality, hospital length of stay, need for prolonged oxygen administration, presence of ROP, NEC and other

outcomes potentially affected by changing oxygen saturation targets were also compared across cohorts.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (Cary, NC, USA). Statistical significance was assessed at the 0.05 level. Descriptive statistics were calculated for all variables of interest and included medians and interquartile ranges and counts and percentages, when appropriate. Categorical variables were compared across the three eras using the Chi-square test. Normality of continuous variables was assessed using histograms, normal probability plots and through the Anderson–Darling test for normality. The distribution of continuous variables was compared across the three eras using Kruskal–Wallis tests.

Since there were differences found between the three eras (Table 1), an adjusted analysis was performed to control for these differences and potential confounders. This adjusted model included all variables that were found to be different across the three eras (Table 1, $P < 0.20$), as well as variables that were associated with developing pulmonary hypertension (Table 3, $P < 0.20$) or thought to be clinically relevant and had sufficient sample size (missing $< 10\%$ observations). In instances of collinearity, collinear variables were excluded. For example, in the case of birthweight, small for gestational age status and gestational age, only gestational age and SGA were included as the birthweight is a function of the other two variables. Variables that were thought to be caused by PH or part of the PH treatment (for example, oxygen on day of life 28, oxygen at 36 weeks cGA, use of inhalted nitric oxide and so on) were not included in the adjusted analysis. Variables included in the adjusted model were maternal pregnancy induced hypertension, multiple gestation, small for gestational age, gestational age at birth, surfactant in delivery room, 5- min Apgar score, IVH grade and invasive infection after day of life 3. Variables were retained in the adjusted analysis regardless of significance to estimate the effect of cohort in the presence of these potential confounders.

To identify risk factors associated with in-hospital mortality, a multivariable logistic model was constructed. Univariable and multivariable logistic regression were used to obtain estimates of association between in-hospital mortality and each candidate predictor. Predictors that were significantly associated with in-hospital mortality at the univariable level ($P < 0.20$) and had sufficient sample size (missing $< 10\%$ of observations), or were felt to be clinically relevant, were included in multivariable modeling. Variables remained in the final model if they were significant at $P < 0.05$. Odds ratios (OR) and 95% confidence intervals (CI) were constructed for both univariable and multivariable models.

RESULTS

Baseline data

Table 1 summarizes patient characteristics between the three cohorts. Prenatal characteristics were similar with respect to rates of multiparity and pregnancy induced hypertension, however, maternal chorioamnionitis rates (Cohort 1: 20 out of 459, 4.4%; Cohort 2: 47 out of 494, 9.5%; Cohort 3: 39 out of 387, 10.1%; $P = 0.002$) and prenatal steroid use (Cohort 1: 392 out of 459, 85.4%; Cohort 2: 442 out of 494, 89.5%; Cohort 3: 351 out of 387, 90.7%; $P = 0.037$) both increased over time.

Neonatal characteristics were also largely similar across cohorts. There were statistically significant trends in the racial makeup of the cohorts with a reduction in the White population and increase in the Asian population over time ($P = 0.007$). Important risk factors for PH and other morbidities in premature infants such as gestational age at birth, small for gestational age status, birth weight, surfactant delivery in the delivery room, and 5 min Apgar score did not trend over time.

Respiratory characteristics and comorbidities

Use of oxygen at day of life 28 was not different across cohorts, however, oxygen use at 36 weeks corrected gestational age decreased over time despite the more stringent SpO_2 requirement (CGA; Cohort 1: 120 out of 459, 34.2%; Cohort 2: 81 out of 494, 21.8%; Cohort 3: 72 out of 387, 24.9%; $P < 0.001$). Post-natal steroid use to treat chronic lung disease of prematurity increased over time (Cohort 1: 46 out of 459, 10.2%; Cohort 2: 109 out of 494, 22.3%; Cohort 3: 79 out of 387, 20.7%; $P < 0.001$).

Rates of PDA ligation decreased significantly over time (Cohort 1: 36 out of 459, 8%; Cohort 2: 17 out of 494, 3.5%; Cohort 3: 8 out of 387, 2.1%; $P < 0.001$) though information on the size or significance of PDAs not referred for surgical ligation was not reviewed. NEC rates also decreased significantly over time (Cohort 1: 40 out of 459, 8.9%; Cohort 2: 20 out of 494, 4.1%; Cohort 3: 9 out of 387, 2.4%; $P < 0.001$). ROP, IVH and invasive infection after day of life three did not trend over time.

Pulmonary hypertension and other outcomes

Table 2 summarizes the measured outcomes. The primary outcome, PH diagnosis, was significantly lower in the higher SpO_2 target cohorts (Cohort 1: 87 out of 459, 19.0%; Cohort 2: 39 out of 494, 7.9%; Cohort 3: 37 out of 387, 9.6%; $P < 0.001$). Although cohort three had a slightly higher rate of PH diagnosis compared with cohort two (9.6 vs 7.9%, $P = 0.382$), these were not statistically different whereas the overall trend for decreased PH diagnosis with increasing saturations was significant ($P < 0.001$). Inhaled nitric oxide use also decreased with increasing saturation target ranges (Cohort 1: 25 out of 459, 2.2%; Cohort 2: 14 out of 494, 2.8%; Cohort 3: 9 out of 387, 2.3%; $P = 0.013$). Other PH medications were used infrequently and did not trend with increasing saturation target ranges. In hospital mortality, weight at initial disposition (discharge or transfer), and initial length of stay (to first transfer or discharge) did not trend over time.

We compared characteristics and outcomes of infants with PH with those who did not develop PH grouping all cohorts together (Table 3) and within cohorts (not shown, not significantly different from grouped data). This table was used to identify potential confounding variables to include in our multivariable analysis (Table 4). Consistent with published studies of risk factors for development of PH in premature infants, we found younger gestational age at birth (26 weeks vs 28 weeks, $P < 0.001$), SGA

Table 2. Outcomes

	Cohort 1, N = *459*	*Cohort 2,* N = *494*	*Cohort 3,* N = *387*	P-*value*[a]
Pulmonary hypertension	87 (19.0%)	39 (7.9%)	37 (9.6%)	< 0.001
In-hospital mortality	73 (15.9%)	66 (13.4%)	47 (12.1%)	0.265
Weight at initial disposition (g)	2468 (1770–2985)	2448 (2003–2910)	2440 (2018–2840)	0.886
Initial length of stay (days)	53 (30–77)	53 (36–77)	53 (36–74)	0.777
Inhaled nitric oxide use	25 (5.4%)	14 (2.8%)	9 (2.3%)	0.028
Sildenafil use	10 (2.2%)	5 (1.0%)	5 (1.3%)	0.309
Bosentan use	2 (0.4%)	1 (0.2%)	1 (0.3%)	0.465

[a]Overall comparison across Cohort 1, 2 & 3; categorical variables compared using Chi-square test; continuous variables compared using Kruskal–Wallis test. Values are presented as *N* (%) or Median (25th–75th).

Table 3. PH vs No PH ($N = 1340$)

	PH, N = *163 (12.2%)*	*No PH,* N = *1177 (87.8%)*	P-*value*
Prenatal data			
Pregnancy-induced hypertension	43 (26.4%)	376 (31.9%)	0.151
Maternal chorioamnionitis	19 (11.7%)	87 (7.4%)	0.059
Prenatal steroids	141 (86.5%)	1044 (88.7%)	0.411
Multiple gestation	43 (26.4%)	370 (31.4%)	0.190
Mother of hispanic origin	10 (6.1%)	127 (10.8%)	0.066
Race of mother			
Black	68 (41.7%)	496 (42.1%)	0.221
White	71 (43.6%)	470 (39.9%)	
Asian	12 (7.4%)	65 (5.5%)	
Missing or unknown	12 (7.4%)	146 (12.4%)	
Neonatal data			
Gestational age at birth	26 (24–27)	28 (26–30)	< 0.001
Small for gestational age	55 (33.7%)	247 (21.0%)	< 0.001
Birthweight	705 (280–917)	1058 (821–1283)	< 0.001
Male	83 (50.9%)	600 (51.0%)	0.989
Surfactant in delivery room	108 (66.3%)	364 (30.9%)	< 0.001
Apgar score < 3 at 5 min	14 (8.6%)	53 (4.5%)	0.026
Respiratory data			
Oxygen on day of life 28	118 (93.7%)	572 (57.0%)	< 0.001
Oxygen at 36 weeks CGA	93 (78.2%)	180 (20.2%)	< 0.001
Use of inhaled nitric oxide	52 (31.9%)	2 (0.2%)	< 0.001
Steroids for CLD	84 (51.5%)	150 (13.0%)	< 0.001
Comorbidity data			
PDA ligation	24 (14.7%)	37 (3.2%)	< 0.001
Necrotizing enterocolitis	9 (5.5%)	60 (5.2%)	0.859
Presence of ROP at discharge			
None/Mild (< stage 2)	91 (75.8%)	954 (97.0%)	< 0.001
Severe (> stage 2)	29 (24.2%)	30 (3.0%)	
IVH grade			
None/Mild (< stage 2)	115 (76.7%)	1040 (94.0%)	< 0.001
Severe (> stage 2)	35 (23.3%)	66 (6.0%)	
Invasive infection after day 3	29 (19.2%)	52 (4.7%)	< 0.001
Outcome data			
In-hospital mortality	54 (33.1%)	132 (11.2%)	< 0.001
Weight at initial disposition	2010 (1010–3325)	2455 (2044–2895)	0.172
Initial length of stay	53 (15–105)	53 (36–74)	0.432
Inhaled nitric oxide use	47 (28.8%)	1 (0.1%)	< 0.001
Sildenafil use	20 (12.3%)	0 (0.0%)	< 0.001
Bosentan use	4 (2.5%)	0 (0.0%)	< 0.001

Abbreviations: CGA, corrected gestational age; CLD, chronic lung disease; GI, gastrointestinal; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus (treatment/closure includes ibuprofen, indomethacin, surgical ligation and transcatheter device closure); ROP, retinopathy of prematurity. Pooled characteristics and outcomes of all three cohorts dichotomized by PH diagnosis or no PH diagnosis using Chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Table 4. Unadjusted and adjusted effect of cohort on diagnosis of pulmonary hypertension

	Unadjusted		*Adjusted*[a]	
	Odds ratio (95% CI)	P-*value*	*Odds ratio (95% CI)*	P-*value*
Cohort				
Cohort 1	Ref.	–	Ref.	–
Cohort 2	0.37 (0.24–0.54)	< 0.001	0.17 (0.10–0.30)	< 0.001
Cohort 3	0.45 (0.24–0.54)	< 0.001	0.24 (0.13–0.42)	< 0.001

Abbreviation: CI = confidence interval. [a]Adjusted for all variables that were significantly associated with developing pulmonary hypertension at the univariate level ($P < 0.20$ in Table 3) and had sufficient sample size (missing < 10% of observations), or were felt to be clinically relevant. Variables adjusted for were maternal pregnancy induced hypertension, maternal chorioamnionitis, prenatal steroids, multiple gestation, small for gestational age, gestational age at birth, mother of Hispanic, race, surfactant in delivery room, Apgar score at 5 min < 3, steroids for CLD, PDA ligation, necrotizing enterocolitis, IVH grade ⩾ 2 and invasive infection after day of life 3. Unadjusted and adjusted effect of cohort (that is, SpO_2 saturation target range) on diagnosis of pulmonary hypertension.

status (33.7 vs 21%, $P < 0.001$), and lower birthweight (705 gm vs 1058 gm, $P < 0.001$) to be more common in infants diagnosed with PH in comparison with their non-PH counterparts. We also found that infants with PH were more likely to have received surfactant in the delivery room (66.3 vs 30.9%, $P < 0.001$) or have had a 5- min Apgar scores < 3 (8.6 vs 4.5%, $P = 0.026$). Infants with PH were more likely to require oxygen on day of life 28 (93.7 vs 57%, $P < 0.001$), at 36 weeks CGA (78.2 vs 20.2%, $P < 0.001$), or receive inhaled nitric oxide (31.9 vs 0.2%, $P < 0.001$) or steroids for chronic lung disease (51.5 vs 13.0%, $P < 0.001$). PDA ligation (14.7 vs 3.2%, $P < 0.001$), severe ROP (24.2 vs 3%, $P < 0.001$), severe IVH (23.3 vs 6%, $P < 0.001$), and invasive infection after day of life 3 (19.2 vs 4.7%, $P < 0.001$) were all associated with PH diagnosis while NEC was not associated with PH in our data set. In-hospital mortality was almost three-fold higher in infants with PH (33.1 vs 11.2%, $P < 0.001$) in univariate modeling and this association between PH diagnosis and mortality remained on multivariable testing while controlling for potential confounders (OR = 3.36; 95% CI: (2.04–5.55), $P < 0.001$). Unsurprisingly, PH-specific medication use was almost exclusively in the PH population. Hospital length of stay and weight at initial disposition (discharge or transfer) were not different between PH and no PH groups.

Our primary outcome, odds of developing PH based on cohort, is shown in Table 4 in both unadjusted and adjusted models. In the unadjusted model, the odds ratio (OR) for developing PH in Cohort 2 was 0.37 (95% CI: (0.25–0.55), $P < 0.001$) and in Cohort 3 was 0.45 (95% CI: (0.30–0.68), $P < 0.001$) using Cohort 1 as the reference, demonstrating a significantly lower odds of developing PH in the later cohorts. The effect of controlling for variables that were different among cohorts, different between PH and no PH groups, and those that were thought to be clinically relevant, was to strengthen the relationship between cohort and PH diagnosis. Variables adjusted for were maternal pregnancy induced hypertension, maternal chorioamnionitis, prenatal steroid use, multiple gestation, small for gestational age status, gestational age at birth, mother of Hispanic origin, maternal race, surfactant in delivery room, 5-minute Apgar score < 3, steroids for CLD, PDA ligation, necrotizing enterocolitis, IVH grade ⩾ 2 and invasive infection after day of life 3. The odds of developing PH in Cohort 2 was 0.17 (0.10–0.30, $P < 0.001$) and in Cohort 3 was 0.24 (0.13–0.42, $P < 0.001$), when controlling for these variables.

DISCUSSION

To our knowledge, this is the first publication investigating the effect of changes in SpO_2 targeting on the incidence of PH in premature infants. In our large, community-based, tertiary NICU,

we found that incidence of PH decreased in association with increased SpO_2 target range. Our findings on PH incidence are congruent with the observed improvement in mortality with higher SpO_2 targets described in large SpO_2 targeting trials.[18,23] The findings support the possibility that the reduced mortality in these studies (excluding the Canadian Oxygen Trial[20] as PH patients were excluded at time of enrollment) may be related to reduction in incidence of PH.

In-hospital mortality was not statistically different across our three cohorts. As with other published reports, though, PH diagnosis was a significant independent risk factor for mortality in our population increasing the odds of death by over 3-fold in our multivariable model.[1,4,5] Gestational age at birth and SGA status have repeatedly been shown to be strong predictors of developing PH and we also found that in our analysis (data not shown).[29] It is worth special mention that our cohorts did not vary with respect to these important risk factors.

Other factors that may impact PH incidence were also largely similar across the three cohorts, though there were three differences that warrant discussion. We found increased use of prenatal steroids and increased maternal chorioamnionitis over time, however, on multivariable analysis, neither of these factors was associated with PH diagnosis. In addition, there was no difference in prenatal steroid use or chorioamnionitis diagnosis between those with PH and those without PH. We extensively sought out an explanation for our finding of increased chorioamnionitis rates across cohorts through investigations with obstetrics, perinatology, and pathology departments at our hospital and could not identify an explanation. There was no change in definition, no increase in placental specimens submitted to pathology for review, and no identifiable change in practice. It is worthy of note that chorioamnionitis rates increased while PH diagnoses fell so the likelihood of interplay for that variable is low. Post-natal steroid use did, however, go up over time and could be protective. It could, also, be part of a treatment strategy. Because we did not know the timing of steroid use with respect to PH diagnosis, we included it in our model of potential confounders and, when adjusted for, did not weaken the link between cohort and PH diagnosis.

Unexpectedly, we found that oxygen use at 36 weeks CGA was lower in the higher SpO_2 target range cohorts in contrast to the SUPPORT trial.[18] One possible explanation for this finding is that reduction in intermittent hypoxic episodes in the higher saturation groups may have a positive effect on lung health.[6] Another contributor could be greater efforts aimed at adherence to oxygen saturation targets in our NICU from 2012 onward in response to emerging awareness of the importance of SpO_2 targeting.

The use of PDA ligation decreased significantly over time. This may reflect a reduction in the incidence of hemodynamically significant PDA due to increased oxygen saturations—a finding suggested by Inomata *et al*. and consistent with oxygen's role in inducing ductal closure.[22,30] This, in turn, might lead to a reduction in shear stress on the pulmonary arterial endothelium and result in lower rates of PH. Another explanation that must be considered, though, is that clinical practice in this NICU has fallen away from ductal ligation in most cases. We must, therefore, consider the possibility that a reduction in PDA ligation led to a reduction in PH, not the increase in SpO_2 target range. However, when controlling for PDA ligation (among other potential confounders) on multivariable testing, the odds of developing PH went down compared to the unadjusted model so it does not appear that reduction in PDA ligation led to the reduction in PH diagnosis.

In contrast to the experience of Manley *et al*.[19] we experience, we did not find any significant change in the rate of ROP diagnosis or severity with increased SpO_2 target range. This is an important finding as concern related to risk of oxygen on ROP development is one of the most often cited rationales for maintaining lower saturation targets. Interestingly, PH was associated with higher rates of more severe ROP in our study population, likely related to shared risk factors though we cannot exclude a causal relationship.

This retrospective cohort study is strengthened by the large number of included patients with 1340 severely premature infants cared for in a single center. A consistent group of neonatologists and pediatric cardiologists cared for these patients over this time period which serves to lessen variability in diagnostic criteria and clinical care and help isolate the impact of the SpO_2 target range. While our population is drawn from a single center, it is similar to previously published series with respect to risk factors for PH and outcomes. We, therefore, feel it is a representative group and our findings are likely to be generalizable to other centers.

A significant limitation of this research is the absence of a strict diagnostic criterion for PH. Cardiac catheterization, the gold standard for PH diagnosis, is not performed in infants at Northside Hospital and was only performed in a small subset of the patients after transfer to Children's Healthcare of Atlanta. Echocardiography, while not the gold standard, is the modality most frequently used for PH diagnosis in this patient population. The interpretations of echocardiography in this population is challenging and multiple factors must be considered (post-natal age, systemic blood pressure, cardiac function, presence, magnitude and direction of shunts, anatomic variables such as branch pulmonary stenosis and so on) making the use of a single parameter to rule in or rule out PH impossible. We therefore chose to rely on the clinical judgment of the treating physicians at the time of clinical assessment as the most likely to be accurate gauge of whether PH was present or not. We recognize that there was almost certainly some misallocation of patients; however any errors are likely to be evenly distributed across cohorts. We did not have the ability to retrospectively review echocardiograms from all eras as those in the earlier era are no longer available. A similar study designed prospectively allowing for strict adherence to a research imaging protocol and blinded review of the images and clinical data would be an appropriate next step to avoid this pitfall.

We are limited, most importantly, by the retrospective nature of this research, as well as the separation of the three cohorts over time. Other aspects of neonatal care that changed over the 6 years under review may have impacted PH diagnosis rates. Querying the physicians involved over those years helped to identify changes in unit policies or practice. Those that may have had an impact on these results include use of donor breastmilk, less aggressive medical and surgical treatment of PDA, increased feedback to bedside nurses regarding time babies spent within intended saturation ranges, and increasing use of non-invasive ventilation. We must recognize that these and other changes in neonatology practice may have led to the observed reduction of PH diagnosis, not the change in SpO_2 target range. A prospective, randomized, blinded study would be required to isolate SpO_2 target range from other potential confounders. In the absence of a new trial, the charts and imaging tests of the infants included in the large saturation targeting trials could be reviewed to confirm or refute our finding.

We also recognize that subjects born near the end of the timeframe of their cohort will largely be exposed to the oxygen saturation target range of the subsequent cohort. As we do not know what the critical timeframe for saturation target exposure is, we opted *a priori* to include subjects based on the policy in place on the date of birth. However, to determine if the results would have been changed by splitting the cohorts differently, we re-ran the analysis using cohort assignment based on discharge date (data not shown) and found no significant difference in the outcomes. We also considered whether time spent outside of the NICU at Northside Hospital could have introduced another confounder. We, therefore, performed a separate sub-analysis (data not shown) excluding infants who spent any time at other institutions who may have been exposed to different SpO_2 targets

($n = 35$ born at other institutions who were transferred into Northside Hospital after birth, $n = 200$ transferred out transiently or permanently to other institutions mainly for surgical procedures, and $n = 9$ that met both of these criteria). This sub-analysis resulted in no meaningful change in any of the relevant outcome measures.

CONCLUSION

In our large, retrospective, single-center experience, exposure to higher SpO_2 target ranges was associated with lower rates of PH diagnosis. Reduction in mortality with higher saturation targets observed in other large saturation targeting studies may be related to reduction in the incidence of PH. Further prospective research to confirm this finding is warranted.

CONFLICT OF INTEREST

Dr Kanaan and Ms Huckaby receive research support but no personal remuneration from Eli Lilly and Company and from the Association for Pediatric Pulmonary Hypertension (a non-profit research organization supported by Actelion Pharmaceuticals, Ltd.). The remaining authors declare no conflict of interest.

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