Early Neonatal Oxygen Exposure Predicts Pulmonary Morbidity and Functional Deficits at 1 Year

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Objective To evaluate the predictive value of cumulative oxygen exposure thresholds over the first 2 postnatal weeks, linking them to bronchopulmonary dysplasia (BPD) and 1-year pulmonary morbidity and lung function in extremely low gestational age newborns.

Study design Infants (N = 704) enrolled in the Prematurity and Respiratory Outcomes Program, a multicenter prospective cohort study, that survived to discharge were followed through their neonatal intensive care unit hospitalization to 1-year corrected age. Cumulative oxygen exposure ($Oxygen_{AUC14}$) thresholds were derived from univariate models of BPD, stratifying infants into high-, intermediate-, and low-oxygen exposure groups. These groups were then used in multivariate logistic regressions to prospectively predict post-prematurity respiratory disease (PRD), respiratory morbidity score (RMS) in the entire cohort, and pulmonary function z scores (N = 108 subset of infants) at 1-year corrected age.

Results Over the first 14 postnatal days, infants exposed to high oxygen averaged ≥33.1% oxygen, infants exposed to intermediate oxygen averaged 29.1%-33.1%, and infants exposed to low oxygen were below both cutoffs. In multivariate models, infants exposed to high oxygen showed increased PRD and RMS, whereas infants exposed to intermediate oxygen demonstrated increased moderate/severe RMS. Infants in the high/intermediate groups had decreased forced expiratory volume at 0.5 seconds/forced vital capacity ratio.

Conclusions $Oxygen_{AUC14}$ establishes 3 thresholds of oxygen exposure that risk stratify infants early in their neonatal course, thereby predicting short-term (BPD) and 1-year (PRD, RMS) respiratory morbidity. Infants with greater $Oxygen_{AUC14}$ have altered pulmonary function tests at 1 year of age, indicating early evidence of obstructive lung disease and flow limitation, which may predispose extremely low gestational age newborns to increased long-term pulmonary morbidity. *(J Pediatr 2020;223:20-8)*.

Trial registration ClinicalTrials.gov: NCT01435187.

Infants born premature are at high risk for adverse pulmonary outcomes including bronchopulmonary dysplasia (BPD), which has been linked to greater early-childhood pulmonary morbidity, neurodevelopmental impairment, and mortality.[1-3] The pathogenesis of BPD is multifactorial and includes infection, inflammation, mechanical ventilation, and supplemental oxygen therapy.[4] Advances in neonatal care and gentle ventilation strategies have improved neonatal mortality in extremely low gestational age newborns (ELGANs) but have failed to significantly decrease BPD rates, leaving these infants at risk for obstructive lung disease and childhood wheezing disorders.[5-9] Several predictive models of BPD have been developed, but most fail to account for longer-term morbidity in ELGANs.[10] Thus, there is a need to identify early risk factors linked to postdischarge outcomes so investigators can target additional strategies and therapeutics early in the hospital course to those at greatest risk.

AUC	Area under the curve	NICU	Neonatal intensive care unit
BPD	Bronchopulmonary dysplasia	$Oxygen_{AUC14}$	Cumulative oxygen exposure
ELGAN	Extremely low gestational age newborn	PFT	Pulmonary function test
FEF_{25-75}	Forced expiratory flow 25%-75%	PRD	Post-prematurity respiratory disease
$FEV_{0.5}$	Forced expiratory volume at 0.5 seconds	PROP	Prematurity and Respiratory Outcomes Program
FIO_2	Fraction of inspired oxygen	RMS	respiratory morbidity score
FVC	Forced vital capacity	sBPD	Severe bronchopulmonary dysplasia
MAP	Mean airway pressure		
msBPD	Moderate/severe bronchopulmonary dysplasia		

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Supplemental oxygen therapy is a life-saving treatment administered to newborns born premature to maintain adequate oxygen saturations. Infants born premature are especially vulnerable to oxygen-related injury due to immature antioxidant defenses, making them more susceptible to oxidative stress.[11] The duration of supplemental oxygen use has been linked to increased risk of respiratory disease,[1,12] but this classification fails to properly capture the cumulative dose-related toxicity that may be associated with greater fractions of inspired oxygen (FIO_2), even for relatively short periods. Previous studies have described several patterns of oxygen exposure, with some infants requiring high oxygen from birth whereas others initially needing minimal support but worsening in the second postnatal week, termed "pulmonary deterioration."[13,14]

Our previous work defined $Oxygen_{\text{area under the curve (AUC)}}$, an integrated measure of oxygen exposure over time, as a predictor of early childhood pulmonary morbidity in infants without BPD.[15] Other studies have validated the concept as a predictor of BPD at 14 days of life.[16] The aim of this study was to develop oxygen-exposure thresholds to risk-stratify infants at 14 days of age and assess predictive models for BPD and 1-year clinical outcomes (assessed by symptomatology score and infant pulmonary function tests [PFTs]) among a large ELGAN cohort in the Prematurity and Respiratory Outcomes Program (PROP) prospective observational study.

Methods

PROP was a multicenter, prospective study enrolled from 2011 to 2014, conducted under institutional review board approval (ClinicalTrials.gov: NCT01435187). The study design, details, including data-collection forms, and CONSORT diagram, have been previously published.[17,18] Data were collected at 6 study centers: Vanderbilt University, University of California San Francisco, University of Rochester and University at Buffalo, Washington University, Cincinnati Children's Hospital Medical Center, Indiana University, and Duke University. This research was conducted through cooperative agreements with the National Heart, Lung, and Blood Institute and in collaboration with the PROP Steering Committee. There were no significant changes to methods after trial commencement, except for the addition of additional funding for assessment of infant PFTs. ELGANs (N = 835) from 23 0/7 to 28 6/7 weeks of gestational age were enrolled at 6 centers. Maternal and infant demographics and daily flowsheets for nutritional and respiratory data were collected from birth to discharge or 40 weeks of postmenstrual age. Infants who died before the 1-year follow-up were excluded from this analysis and missing values were not imputed. We only included surviving infants in this analysis, reducing a potential bias of increasing FIO_2 requirement preceding an imminent death. The short-term outcome of BPD and its severity classification (mild, moderate, or severe) status was determined at 36 weeks of postmenstrual age by the National Institutes of Health workshop definition.[18,19] Long-term outcomes of post-prematurity respiratory disease (PRD) and respiratory morbidity score (RMS) were determined at 1-year postnatal age by quarterly follow-up questionnaires as previously published.[20] PRD was diagnosed if there were positive responses on at least 2 caregiver post-discharge questionnaires to the following: (1) hospitalization for respiratory indication, (2) home respiratory support, (3) respiratory medication administration, and/or (4) respiratory symptoms without a cold. RMS was graded on a severity scale in one of three mutually exclusive categories: (1) Severe, if there were ≥2 respiratory hospitalizations, home supplemental O_2 after 3 months or any home mechanical ventilation, systemic steroid exposure or pulmonary vasodilators, or symptoms despite inhaled corticosteroid use; (2) Moderate/mild, if one hospitalization, home oxygen <3 months corrected age or tracheostomy without ventilation, any inhaled corticosteroid or bronchodilator exposure, or symptoms in ≥2 questionnaires; or (3) Minimal/none for all other cases.

$Oxygen_{AUC}$ was calculated from the daily respiratory flowsheet data, which recorded FIO_2, respiratory support mode, and applied airway pressure or cannula flow once daily (at noon) through the first 28 days of life. The following equation was used for each observed data point: $Oxygen_{AUC}$ = Hrs*($Effective_{FIO2}$-21), where Hrs was the number of hours between observations (24 in this case) and $Effective_{FIO2}$ was the FIO_2 delivered to the infant, corrected for nasal cannula using established tables if applicable.[21] For example, an infant on 50% effective FIO_2 generated $Oxygen_{AUC}$ = 24*(50-21) = 696 percent*hours for that calendar day. We integrated $Oxygen_{AUC}$ from birth to several different time points between 1 and 28 days of life, at times back-calculating the effective FIO_2 over a given time period by rearranging the aforementioned equation. Mean airway pressure was similarly calculated as MAP_{AUC} = Hrs * $Effective_{MAP}$ and integrated over the same time points, using pressure estimates for applied pressure while on nasal cannula if applicable.[22]

After analyzing unadjusted receiver operating characteristic curves at each time point, we chose to model BPD using $Oxygen_{AUC}$ at 14 days of postnatal age ($Oxygen_{AUC14}$) to optimize early detection and predictive probability and include the second postnatal week to capture pulmonary deterioration.[13,14,16] A validation cohort of 97 infants (80 plus their siblings if multiple gestation) was selected randomly from the full cohort, in a manner that reduces random-effects related to multiple births. The remaining subjects were used in the modeling cohort where fixed-effects logistic regression models were created to determine $Oxygen_{AUC14}$ cutoffs for severe bronchopulmonary dysplasia (sBPD) and moderate/severe bronchopulmonary dysplasia (msBPD), using an SAS macro (SAS Institute, Cary, North Carolina) to select an $Oxygen_{AUC14}$ cutoff with ≥80% specificity for the selected BPD outcome. Based on these cutoffs, infants were divided into 3 mutually exclusive groups: high oxygen (above the sBPD cutoff), intermediate oxygen (above the msBPD cutoff and below the sBPD cutoff), and low

oxygen (below both cutoffs). We performed all analyses independent of study center to increase generalizability.

Infant PFTs were performed in a subset of PROP subjects with parental consent for sedation and testing, excluding infants with airway anomalies or clinical illness. Testing used the nSpire Infant Pulmonary Lab (nSpire, Inc, Longmont, Colorado) or the BabyBox device (Carefusion Respiratory Diagnostics, Yoma Linda, California) depending on study center. The protocol used a raised volume rapid thoracoabdominal compression technique[23] and body plethysmography,[24] adhering to American Thoracic Society guidelines.[25,26] The devices used for infant PFTs are cleared by the US Food and Drug Administration, and some centers perform infant PFTs as part of clinical care, including use of choral hydrate, which causes sedation without affecting respiratory effort.[27-29] Therefore, the institutional review boards at the individual PROP sites considered this a minimal risk study. In brief, infants were sedated with chloral hydrate (75-100 mg/kg by mouth). Once adequate sedation was achieved, functional residual capacity was measured by body plethysmography. To measure forced expiratory flows, a mask sealed with therapeutic putty was placed around the infant's mouth and nose. The lungs were inflated to 30-cm H_2O pressure 2 or 3 times to induce chest wall relaxation. The lungs were then inflated again to 30-cm H_2O pressure, an inflatable jacket that surrounded the chest and abdomen was rapidly inflated, and the pressure in the cuff was maintained until expiratory flow fell to zero. This maneuver was repeated with increasing jacket pressure until flow limitation was achieved. Pulmonary function parameters were again measured after albuterol administration via metered dose inhaler (4 puffs) with parental consent. Acceptable research-quality infant PFTs demonstrated at least 2 reproducible flow–volume curves whose sum of forced vital capacity (FVC) and forced expiratory flow (FEF) between 25% and 75% of FVC were within 10% of each other. Albuterol responders were defined as greater than 2 SDs above previously published standards (pre-vs postalbuterol) for either forced expiratory volume at 0.5 seconds ($FEV_{0.5}$; ≥12% change) or FEF_{25-75} (≥24% change), excluding infants with a ≥10% decrease in FVC.[30]

Statistical Analyses

Bivariate analyses and logistic regressions were performed with SAS 9.4 (SAS Institute). Univariate analyses to establish $Oxygen_{AUC}$ thresholds are described as mentioned previously. Multivariate analyses were performed using forward selection of 14-day known clinical variables with $p_{entry} = 0.05$ and $p_{staying} = 0.1$ for PRD (yes/no) and RMS (none/mild, moderate, or severe) including gestational age in all models. The proportional OR was not violated. Comparisons between oxygen-exposure groups were made using *t* tests or ANOVA where appropriate.

Because infant PFTs could only be performed on a subset of study subjects, the high- and intermediate-oxygen groups were combined to increase statistical power. The raw pulmonary function variables were converted to z scores based on previously published reference equations depending on the device used for testing at each study center.[31-33]

Results

Of 835 infants originally enrolled, 704 were included in the final analyses (87 died, 30 withdrew, 14 were missing BPD diagnosis). No changes in trial outcomes occurred after commencement. Demographic, maternal, delivery room, and neonatal intensive care unit (NICU) clinical data for infants in the high-, intermediate-, and low-oxygen exposure groups are shown in **Table I**.[34] Infants in the high-oxygen group were less likely to receive antenatal steroids than the low/intermediate groups but had no other significantly different maternal or pregnancy characteristics. In addition, infants in the high/intermediate group had lower gestational age, birth weight, and greater rates of intrauterine growth restriction compared with the low-oxygen group. Delivery room management with intubation, surfactant, and epinephrine and delivery room hypothermia also were more frequently observed in infants in the high/intermediate oxygen group. Finally, infants who had high exposure required more mechanical ventilation in the first 2 weeks (median 14/14 days), whereas infants with intermediate and low oxygen exposure were intubated less often (median 10/14 days and 2/14 days, respectively).

Receiver operating characteristic curves for unadjusted $Oxygen_{AUC14}$, for BPD, msBPD, and sBPD at 14 days of age are displayed in **Figure 1**, Panel 1. $Oxygen_{AUC}$ was highly predictive of all BPD severities, with AUC ranging from 0.801 to 0.901. We selected cutoffs targeting >80% specificity to define 3 mutually exclusive groups: high oxygen (N = 136; $Oxygen_{AUC14} \geq 4080$; >33.1% average FIO_2), intermediate oxygen (N = 92; $Oxygen_{AUC14} \geq 2712$; 29.1%-33.1% average FIO_2), and low oxygen (N = 476; $Oxygen_{AUC14} < 2712$, 21.0%-29.0% average FIO_2). We applied these cutoffs to our internal validation cohort with similar sensitivity and specificity (**Table II**; available at www.jpeds.com). The predicted probability of each BPD outcome is plotted against 14-day average FIO_2 (back-calculated from $Oxygen_{AUC14}$) and displayed in **Figure 1**, Panel 2. Of note, we calculated integrated mean airway pressure (MAP_{AUC14}) similarly to $Oxygen_{AUC14}$, but adding this variable did not significantly strengthen our models (data not shown).

To examine patterns of oxygen exposure over time, we plotted effective inspired FIO_2 for each group over the first 28 postnatal days (**Figure 2**; available at www.jpeds.com). Infants receiving high oxygen experienced greater supplemental oxygen use over the first 28 days compared with lower groups ($P < .0001$), a pattern also observed in intermediate vs low for days 3-28 ($P < .001$). Infants in the high-oxygen group also had the greatest frequency and largest degree of pulmonary deterioration, defined as the increase in FIO_2 from week 1 to week 2 (median increase 8.9%), also shown graphically (**Figure 2**).

Table I. Demographic data and clinical outcomes of the PROP ELGAN population

Parameter	Oxygen-exposure group			ANOVAx	Post-hoc comparisons	
	Low (N = 476)	Intermediate (N = 92)	High (N = 136)	*P* value	Intermediate vs high	Low vs intermediate
Infant demographics						
Gestational age, wk, mean (SD)	27.2 (1.2)	26.2 (1.3)	25.5 (1.4)	<.0001	<.0001	<.0001
Male sex	239 (50.2%)	49 (53.2%)	72 (52.9%)	.77	.96	.59
Race/ethnicity				.10	.38	.42
White, Non-Hispanic	228 (47.9%)	48 (52.2%)	70 (51.5%)			
Black	167 (35.1%)	34 (37.0%)	56 (41.2%)			
White, Hispanic	53 (11.1%)	8 (8.7%)	5 (3.7%)			
Other	28 (5.9%)	2 (2.2%)	5 (3.7%)			
Birth weight, g (SD)	993 (220)	801 (167)	757 (173)	<.0001	.059	<.0001
IUGR*	10 (2.1%)	10 (10.9%)	11 (8.1%)	<.0001	.48	<.0001
Multiple gestation	132 (27.7%)	19 (20.6%)	31 (22.8%)	.24	.70	.16
Maternal characteristics						
Gestational diabetes	46 (9.7%)	12 (13.0%)	13 (9.6%)	.59	.41	.33
Asthma	37 (7.8%)	6 (6.5%)	16 (11.8%)	.26	.18	.67
Antenatal steroids	419 (88.0%)	77 (83.7%)	107 (78.6%)	.02	.35	.25
Chorioamnionitis – histologic pathology	74 (15.6%)	13 (14.1%)	27 (19.8%)	.41	.27	.73
Delivery room interventions						
Intubation	351 (73.7%)	77 (83.7%)	121 (89.0%)	.0003	.24	.04
Surfactant	263 (55.3%)	59 (64.1%)	99 (72.8%)	.0008	.16	.12
Chest compressions	43 (9.0%)	13 (14.1%)	21 (15.4%)	.06	.78	.13
Epinephrine	14 (2.9%)	4 (4.3%)	13 (9.6%)	.004	.14	.48
Temp <36.5°C	114 (24.1%)	33 (35.9%)	59 (43.7%)	<.0001	.24	.02
Respiratory NICU outcomes – first 14 d						
$Oxygen_{AUC}$, median [IQR]	801 [264-1704]	3324 [3000-3600]	6048 [4872-8616]	<.0001	<.0001	<.0001
Effective FIO_2, %, median [IQR]	23.4 [21.8-26.1]	30.9 [29.9-31.7]	39 [35.5-46.7]	<.0001	<.0001	<.0001
MAP_{AUC}, cm H_2O, median [IQR]	73 [53-91]	107 [84-124]	126 [107-144]	<.0001	<.0001	<.0001
Effective MAP, cm H_2O, median [IQR]	5.2 [3.8-6.5]	7.6 [6-8.9]	9 [7.6-10.3]	<.0001	<.0001	<.0001
Pulmonary deterioration – weeks 1 to 2						
Infants with FIO_2 increase, n (%)	194 (40.8%)	52 (56.5%)	106 (77.9%)	<.0001	.0006	.005
Change in FIO_2, median [IQR]	0.0 [–2.2 to 1.3]	2.1 [–4.5 to 6]	8.9 [1.2-16.6]	<.0001	<.0001	.03
Change in MAP, median [IQR]	−1 [–2.3 to 1]	−0.3 [–1.3 to 0.8]	0.7 [–0.7 to 2.2]	<.0001	.0002	.0002
Mode of respiratory support – first 14 d of life, d, median [IQR]				<.0001	<.0001	<.0001
Endotracheal tube	2 [1, 5]	10 [4, 14]	14 [12, 14]			
Conventional ventilation	2 [1, 4]	6 [2, 11]	5 [2, 9]			
High-frequency ventilation	0 [0, 0]	0 [0, 4]	7 [0, 11]			
Nasal CPAP	2 [0, 6]	0 [0, 4]	0 [0, 1]			
Nasal cannula	3 [0, 10]	0 [0, 1]	0 [0, 0]			
Nonrespiratory NICU outcomes						
Sepsis confirmed by Blood culture	78 (16.4%)	20 (21.7%)	30 (22.0%)	.20	.95	.21
Prophylactic indomethacin	107 (22.5%)	36 (39.1%)	57 (41.9%)	<.0001	.68	.0008
PDA diagnosed by echocardiography	197 (41.4%)	56 (60.9%)	96 (70.6%)	<.0001	.13	.0006
PDA treated with surgical ligation	20 (4.2%)	9 (9.8%)	27 (19.9%)	<.0001	.04	.03
Necrotizing enterocolitis (Bell stage 2 or 3)	33 (6.9%)	10 (10.9%)	12 (8.8%)	.38	.61	.19
Necrotizing enterocolitis (surgical)	16 (3.3%)	4 (4.4%)	9 (6.6%)	.24	.47	.64
Stage ROP ≥2	89 (18.6%)	37 (40.2%)	79 (58.0%)	<.0001	<.0001	<.0001
Surgical ROP	15 (3.2%)	9 (9.8%)	21 (15.4%)	<.0001	.21	.004
Anti-VEGF treatment	2 (0.4%)	4 (4.4%)	9 (6.6%)	<.0001	.47	.0007
Pulmonary hypertension	18 (3.8%)	9 (9.8%)	27 (19.9%)	<.0001	.04	.01
Growth velocity, g/kg/d, mean (SD)†						
Non-IUGR	16.3 (3.0)	15.7 (2.9)	14.9 (3.8)	<.0001	.15	.09
IUGR	18.7 (3.1)	16.6 (4.1)	13.1 (3.6)	.005	.056	.21
Short-term respiratory outcomes						
BPD (yes/no)	193 (40.5%)	86 (93.4%)	135 (99.2%)	<.0001	.01	<.0001
msBPD	103 (21.6%)	63 (68.4%)	110 (80.8%)	<.0001	.03	<.0001
sBPD	70 (14.7%)	38 (41.3%)	83 (61.0%)	<.0001	.003	<.0001
Postdischarge risk factors						
Long-term respiratory outcomes						
Post-prematurity respiratory disease	291 (61.1%)	64 (69.6%)	108 (79.4%)	.002	.21	.31
Respiratory morbidity severity (moderate/severe)	294 (65.1%)	70 (79.6%)	114 (87.0%)	<.0001	.14	.009
Respiratory morbidity severity (severe)	119 (26.4%)	32 (36.4%)	68 (51.9%)	<.0001	.02	.056
Public insurance anticipated	297 (62.4%)	61 (66.3%)	96 (70.6%)	.19	.49	.47
Parent with asthma	104 (21.9%)	22 (23.9%)	46 (33.8%)	.02	.10	.66

(*continued*)

Table I. Continued

Parameter	Oxygen-exposure group			ANOVAx	Post-hoc comparisons	
	Low (N = 476)	Intermediate (N = 92)	High (N = 136)	*P* value	Intermediate vs high	Low vs intermediate
Potential postdischarge smoke exposure‡	150 (31.5%)	27 (29.4%)	43 (31.6%)	.91	.71	.68

CPAP, continuous positive airway pressure; *IUGR*, intrauterine growth restriction; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *VEGF*, vascular endothelial growth factor.
Oxygen-exposure groups are shown with ANOVA comparisons between all 3 groups (low, intermediate, and high). Post-hoc comparisons are shown between intermediate/high and low/intermediate groups.
*IUGR defined as <10th percentile from gestational age-specific fetal growth curves by Fenton.[34]
†Growth velocity over last 28 days before 36 weeks' postmenstrual age defined as ([weight 36 weeks – weight 32 weeks]/(([weight 36 weeks + weight 32 weeks]/2)/1000 g/kg))/(days 36 weeks – days 32 weeks).
‡Considered positive if any of the following were answered yes: maternal smoking during pregnancy, peer smoking during pregnancy, smoking allowed in some or all parts of home, smoking allowed in vehicle.

Adjusted logistic regression results for PRD and RMS using oxygen exposure groups and known 14-day clinical variables are shown in Table III. Infants in the high-oxygen group had increased odds of PRD and moderate/severe RMS compared with the infants in the low-oxygen group. Infants in the intermediate-oxygen group had greater odds for moderate/severe RMS compared with infants in the low-oxygen group but similar odds of PRD. Male sex, black race, delivery room surfactant, and prophylactic indomethacin also increased odds of PRD and RMS, whereas gestational age was not predictive. The only significant postnatal risk factor was tobacco smoke exposure for PRD, with a strong trend for moderate/severe RMS.

Pulmonary function testing was performed on a subset (N = 108) infants at an average of 12.3 months' corrected age with comparisons made between low- and high/intermediate-oxygen groups (Table IV). Of this cohort of 108 infants, 6 infants experienced an adverse event (5.6%). Only 1 of these events was serious and consisted of upper airway obstruction. The high/intermediate group had lower birth weight and gestational age but no other demographic differences. Among oxygen-exposure groups, infants in the high/intermediate groups had lower $FEV_{0.5}/FVC$ ratios, suggesting obstructive lung disease. In addition, there was a trend for lower FEF_{75} in the infants in the high/intermediate oxygen groups, although both groups show flow limitation compared with expected values. Notably, this flow limitation was not reversible after albuterol

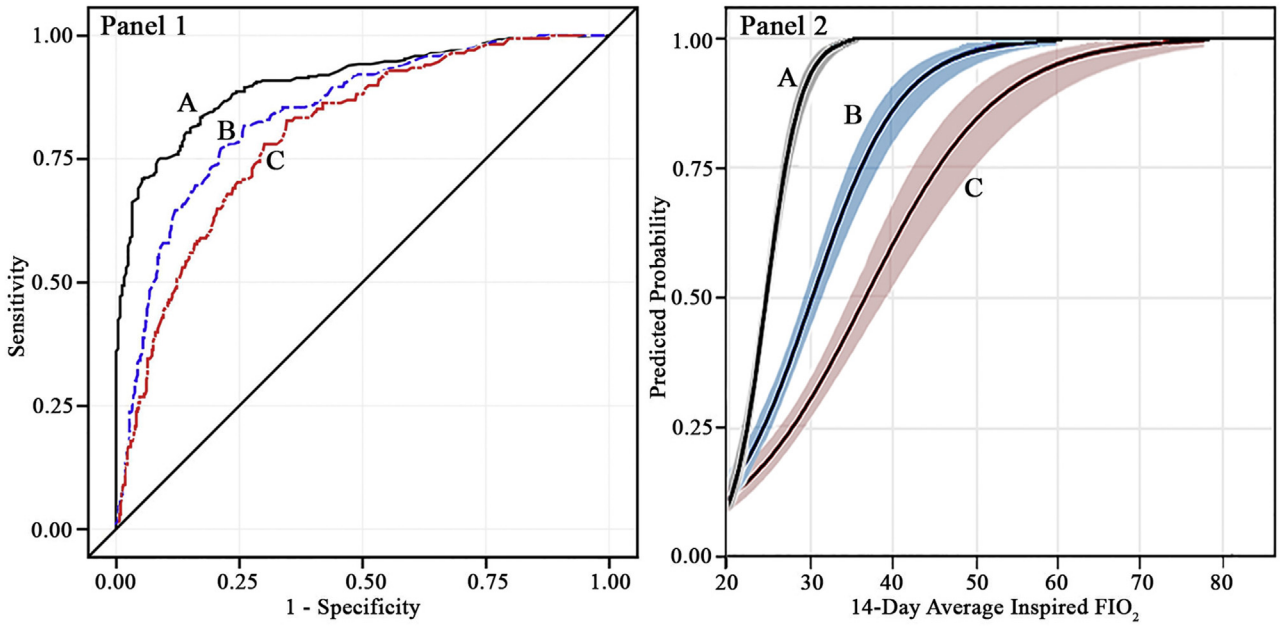

Figure 1. $Oxygen_{AUC14}$ predicts BPD at 14 days of life. **Panel 1**, Receiver operating characteristic curves for each outcome: *A*, any BPD diagnosis, AUC 0.901; *B*, moderate/severe BPD, AUC 0.841; and *C*, severe BPD, AUC 0.801. **Panel 2**, Predicted probabilities and 95% CIs of 14-day average FIO_2 for each outcome: *A*, any BPD; B, moderate/severe BPD; and *C*, severe BPD.

Table III. Logistic regression for long-term outcomes

Parameters	PRD	RMS (moderate/mild or severe)
Gestational age (per week)	1.03 [0.89-1.19]	1.05 [0.91-1.23]
Oxygen exposure group		
High	2.17 [1.26-3.73]	3.08 [1.68-5.66]
Intermediate	1.35 [0.79-2.3]	1.92 [1.07-3.46]
Low	1.00 [ref]	1.00 [ref]
Male sex	1.99 [1.41-2.81]	1.67 [1.17-2.39]
IUGR	–	–
Race		
White, non-Hispanic	1.00 (ref)	1.00 (ref)
Black	1.74 [1.15-2.64]	2.15 [1.42-3.27]
Hispanic	0.93 [0.43-1.98]	0.83 [0.38-1.79]
Other	0.71 [0.39-1.28]	0.84 [0.47-1.51]
Delivery room surfactant	1.50 [1.05-2.13]	1.62 [1.12-2.33]
Prophylactic indomethacin	1.53 [1.01-2.32]	1.79 [1.14-2.8]
Public insurance anticipated	1.46 [0.99-2.16]	–
Potential postnatal smoke exposure	1.59 [1.06-2.38]	1.49 [0.99-2.24]

Multivariate analysis for PROP ELGANs (N = 704) for outcomes of PRD and moderate/mild or severe RMS. Clinical variables were included if known by 14 days' postnatal age and met inclusion criteria for forward selection. The high-oxygen group had increased odds for both PRD and RMS while controlling for other variables. Infants in the intermediate-oxygen group had greater odds of RMS but similar odds for PRD.

Table IV. Infant pulmonary function testing at 1-year corrected age

Variables	Low oxygen (N = 65)	Intermediate/high oxygen (N = 43)	*P* value
Age at PFT (corrected months)	13.8 (2.4)	13.7 (2.4)	.95
Weight at PFT, kg	9.5 (1.3)	9.0 (1.5)	.08
Gestational age, wk	27.1 (1.2)	26.0 (1.2)	<.0001*
Birth weight, g	1000 (202)	800 (198)	<.0001*
Height, cm	75.2 (4.6)	73.8 (4.9)	.12
Male sex, n (%)	32 (49%)	23 (54%)	.66
Baseline respiratory rate (min^{-1})	35.2 (9.1)	33.4 (9.1)	.37
Parent with asthma (%)	20%	23%	.68
Potential smoke exposure, n (%)	20 (30.8%)	16 (37.2%)	.49
Pulmonary function testing			
FRC z score	0.21 (1.44)	0.48 (1.39)	.38
$FEV_{0.5}$ z score	−0.56 (1.06)	−0.65 (1.20)	.71
FVC z score	−0.72 (0.97)	−0.41 (0.75)	.11
$FEV_{0.5}$/FVC z score	0.34 (1.30)	−0.37 (1.31)	.01*
FEF_{25-75} z score	−0.36 (1.51)	−0.91 (1.81)	.12
FEF_{75} z score	−0.98 (1.43)	−1.38 (1.58)	.27
Tpef/Te z score	−0.09 (1.00)	−0.34 (1.11)	.23
Respiratory system resistance z score	−0.19 (1.15)	−0.23 (1.19)	.89
Respiratory system compliance z score	−1.03 (1.12)	−1.04 (1.29)	.98
Bronchodilator responders, n (%)	4/38 (11%)	1/27 (4%)	.31

FRC, functional residual capacity; *Tpef/Te*, Time to Peak Expiratory Flow to Total Exhalation Time.
Infants in the low-oxygen group were compared with a combined intermediate/high-oxygen group. There were no differences in baseline demographic characteristics. Infants in the intermediate/high-oxygen group had greater FRC% predicted and lower z scores for $FEV_{0.5}$/FVC with a trend for lower FEF_{75}, indicating greater obstructive pulmonary disease with increased neonatal oxygen exposure.
*$P < .05$

administration, as only 7% of the cohort were bronchodilator responders. Finally, there were no differences in baseline resistance, compliance, or albuterol response rates between groups.

Discussion

This analysis of 704 ELGANs in the PROP cohort supports the hypothesis that greater $Oxygen_{AUC14}$ is associated with worse respiratory outcomes during the first year of life, in a dose-dependent manner. Using $Oxygen_{AUC}$ can define evidence-based thresholds to risk-stratify infants into 3 groups at 14 days' postnatal age. These groupings prospectively predict both subjective (BPD, PRD, RMS) and objective (PFT) pulmonary outcomes. We found that our high-oxygen group had increased BPD, PRD, and RMS, whereas the intermediate exposure group had increased BPD and RMS with similar PRD.

BPD, PRD, and RMS are all characterizations of chronic lung disease of prematurity with multifactorial etiologies. Previous work from this cohort identified gestational age, male sex, intrauterine growth restriction, and race as antenatal risk factors for PRD and RMS, suggesting that, like BPD, genetic factors play a significant role in its pathogenesis.[20] That same study identified several postnatal risk factors, including BPD, as associated with PRD.[20] Interestingly, BPD was the only variable that incorporated supplemental oxygen exposure, which cannot be determined until 36 weeks' corrected age using most current definitions. In our analysis, $Oxygen_{AUC14}$ was the strongest predictor for all BPD levels, and its significance held in long-term multivariate models, indicating a role in early prediction of pulmonary outcomes. In addition, the infants exposed to the highest oxygen are at greatest risk for other secondary morbidities, including pulmonary hypertension, retinopathy of prematurity, and growth delay (Table I). Although $Oxygen_{AUC14}$ is not the only clinical variable or biomarker that predicts BPD, its ability to predict longer-term outcomes at 2 weeks of life highlights the potential of $Oxygen_{AUC14}$ to be used as a clinical tool, perhaps in combination with other well-established biomarkers and calculators, to define risk and screen for other secondary morbidities related with prematurity.

The longitudinal tracking of oxygen exposure over time also reveals patterns putting infants at highest risk. The first 2 weeks of preterm life are associated with risk for rapid destabilization requiring increased respiratory support.[35] The reasons why some ELGANs maintain adequate gas exchange and oxygen saturations whereas others require supplemental oxygen remain unclear, as are the reasons for deterioration in the second postnatal week. Greater birth weight and gestational age were associated with less oxygen exposure, suggesting that there is a developmental level the lung must attain to successfully transition to extrauterine life. We acknowledge that early in an infant's neonatal course

the need for greater doses of supplemental oxygen may simply be another marker of disease severity, similar to the need for mechanical ventilation. However, we speculate that oxygen exposure transitions from an indicator of lung immaturity to an exacerbating factor leading to alveolar simplification and airway dysfunction as the premature lung maladapts to its hyperoxic extrauterine environment. Although the exact point where this transition occurs is still unknown, a developmental window of greater susceptibility may occur during the second postnatal week.[14] Infants with high exposure had the greatest frequency and greatest severity of pulmonary deterioration during week 2 with FIO_2, increasing by a median of 8.9%, and MAP only increased 0.7cm H_2O, suggesting that increased oxygen requirement best demarcates pulmonary deterioration. Researchers have proposed adrenoglucocorticoid deficiency, surfactant deficiency, increased hypoxemic events, and cytokine imbalances as possible causes,[36-39] but little progress has been made to attenuate this deterioration. $Oxygen_{AUC14}$ provides a sensitive marker that can be defined at any point in the NICU hospitalization to determine whether future management or therapeutic strategies in decreasing ventilation and oxygen use can attenuate their associated harms in those at greatest risk.

Strengths to this study include the availability of infant PFTs at 1 year of age as an objective measure complementing the clinical outcomes of PRD and RMS. Among oxygen-exposure groups, there was evidence of worse flow obstruction (decreased $FEV_{0.5}$/FVC) in the high/intermediate groups compared with the low-exposure group. Notably, oxygen-exposure classification was an equal or better predictor of flow obstruction than BPD, PRD, or RMS despite these other diagnoses being defined at later time points (data not shown). We speculate this is because although PRD and RMS may partially reflect baseline lung function, infants are more likely to meet diagnostic criteria during illnesses (known to be more severe in former preterm infants), whereas infant PFTs are performed when the infant is well, underscoring the need for robust clinical and physiologic outcomes. These data are consistent with recent reports of increased airflow obstruction in preterm cohorts despite less-invasive ventilation and pulse oximetry.[9] In addition, many of these children born early-preterm are not receiving treatment or focused follow-up despite having significantly decreased baseline spirometry.[8] The low bronchodilator response rate is also notable and suggests that the airway dysfunction in infants born premature is fixed. Initiating bronchodilator therapies in this population should be done judiciously, with discontinuation of treatments that do not show demonstrable benefit and may carry risk of side effects. Other groups using infant PFTs in infants with sBPD close to discharge found 3 different phenotypes (obstructive, restrictive, and mixed), with more robust bronchodilator response rates in the obstructive phenotype.[40] Population selection (only 25% of the PROP infant PFT cohort had sBPD), definition of responsiveness (PROP was stricter), and patient age at testing (NICU vs 1 year old) may account for the differences in the study findings. This study associates early oxygen exposure with infant PFTs, providing an early predictor of airway dysfunction to supplement the clinical outcomes. After discharge, a former infant born premature is potentially exposed to respiratory viruses and environmental factors (tobacco, mold, etc) that can further alter pulmonary development. Taken together, these data indicate ELGANs are suffering from early obstructive pulmonary disease; longer-term follow up of PROP subjects (planned to approximately 10 years of age as part of the Environmental Influences on Child Health Outcomes [ECHO] program) should clarify the natural history of respiratory dysfunction in preterm infants after contemporary NICU care.

We acknowledge limitations to this study, in part due to the retrospective design of this prospective cohort analysis. First, the sampling rate for FIO_2 data was only performed once daily at most centers, which would miss variations happening throughout the day. Other studies have sampled more frequently,[15,16] but this also fails to capture minute-to-minute changes occurring in circumstances such as hands-on care or suctioning. Nonetheless, one PROP study center (Rochester/Buffalo) recorded FIO_2 4 times daily, and after recalculating $Oxygen_{AUC14}$ for 121 infants using the more frequently sampled data, we found that 91% would not change O_2 exposure groups using the cutoffs proposed here. Although more data points would be ideal, our current sampling rate gives a reasonable representation of the infant's overall cumulative oxygen exposure. Although we have a sensitive measure of cumulative oxygen exposure, we could not couple this with real-time oxygen-saturation data to determine whether these infants attained their target saturation ranges, which were left to each individual center's discretion. Although this study was observational, several other landmark studies including STOP-ROP and SUPPORT showed that increasing oxygen exposure (through increasing target O_2 saturations) is associated with increased BPD severity or more parent-reported wheezing, consistent with our results that more oxygen exposure may lead to worse pulmonary outcomes.[41,42] Similarly, surfactant administration and delivery room protocols were not standardized. We also cannot draw any causative relationships between supplemental oxygen exposure and pulmonary morbidity from this cohort and acknowledge that oxygen is rarely delivered without positive pressure. However, cumulative mean airway pressure (MAP_{AUC}) did not perform as well as $Oxygen_{AUC}$ in either univariate or multivariate models (data not shown). Presumably, any intervention that might improve overall lung function also would decrease the need for supplemental oxygen and attenuate pulmonary deterioration, making oxygen a difficult factor to isolate in clinical trials. Finally, there were 2 devices used for pulmonary function testing across the 6 study centers, necessitating the use of different reference equations to compare pulmonary function z scores. Despite controlling for the device, the inherent variability in z scores and low number of available control subjects can make generalization of PFTs difficult.

In conclusion, early cumulative oxygen exposure was associated with short- and long-term morbidity and altered

pulmonary function in a large ELGAN cohort. This effect occurred at doses of oxygen many clinicians deem acceptable. $Oxygen_{AUC}$, a measure of cumulative exposure to supplemental oxygen, can identify high-risk infants early in their neonatal course. The ability for $Oxygen_{AUC}$ to be aggregated and summarized over distinct periods of time (ie, the second postnatal week during pulmonary deterioration) can improve characterization of an infant's neonatal respiratory course and risk profile, which may allow for testing of targeted interventions that improve short- and long-term outcomes. ■

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Appendix

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Table II. Validation of $Oxygen_{AUC}$ cutoffs

Cutoffs	Sensitivity (95% CI)	Sensitivity *P* value modeling vs validation	Specificity (95% CI)	Specificity *P* value modeling vs validation
Intermediate oxygen				
Modeling cohort	63.8% (57.4-69.9)	.89	88.2% (84.6-91.4)	.09
Validation cohort	55.6% (38.1-72.1)		80.3% (68.2-89.4)	
Whole cohort	62.7% (56.7-68.4)		87.2% (83.6-90.2)	
High oxygen				
Modeling cohort	44.6% (37.0-52.5)	.80	90.2% (87.0-92.8)	.33
Validation cohort	34.8% (16.4-57.3)		86.5% (76.6-93.3)	
Whole cohort	43.5% (36.3-50.8)		89.7% (86.7-92.1)	

Modeling (N = 607) and validation (N = 97) cohorts were created from a subset of the entire cohort (N = 704) by randomly selecting 80 infants and including their siblings if they were of multiple gestation. Modeling for the intermediate cutoff was based on msBPD, whereas the high cutoff was based on sBPD. Cutoffs were applied to the validation cohort to assess their sensitivity and specificity, which were not statistically different.

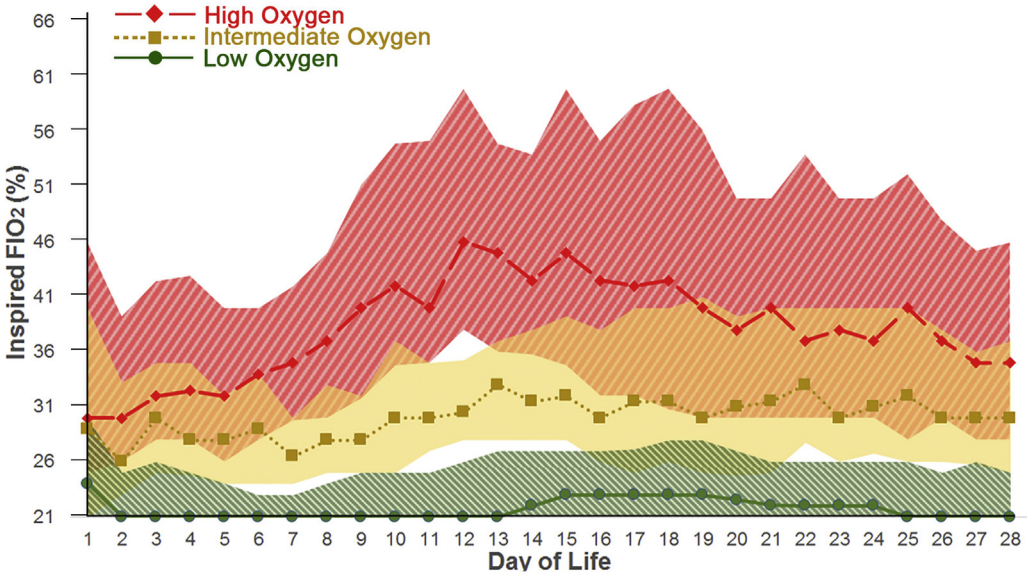

Figure 2. Inspired oxygen over the first 28 postnatal days. ELGANs were classified as having high oxygen (median: *diamonds/dashed line*, IQR: *red shaded area*), intermediate oxygen (median: *squares/dotted line*, IQR: *yellow solid area*), or low oxygen (median: *circles/solid line*, IQR: *green shaded area*). Infants in the high-oxygen group had greater inspired FIO_2 across days 1-28 compared with the intermediate and low groups ($P < .05$ day 1, $P < .002$ thereafter).