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Patterns of Oxygenation, Mortality and Growth Status in the Surfactant, Positive Pressure and Oxygen Trial Cohort

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Abstract

Objective—To characterize actual achieved patterns of oxygenation in appropriate (AGA) versus small (SGA) for gestational age infants randomized to a lower (85–89%) versus higher (91–95%) oxygen saturation target in the Surfactant, Positive Pressure and Oxygen Trial (SUPPORT). To determine the association between achieved oxygen saturation levels and survival in AGA and SGA infants enrolled in SUPPORT.

Study design—Median oxygen saturation and intermittent hypoxemia events (<80%, 20sec–5min) were documented in 1054 infants of 24–27 6/7wks gestation while receiving supplemental oxygen during the first three days of life.

Results—Lower target SGA infants had the lowest oxygen saturation and highest incidence of IH during the first three days of life. The lowest quartile of oxygen saturation (<92%) during the first three days of life was associated with lower 90 day survival for both AGA and SGA infants. An increased incidence of IH events during the first three days of life was associated with lower 90 day survival only in SGA infants.

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The authors declare no conflicts of interest.

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Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov): NCT00233324

Conclusion—Lower achieved oxygen saturation during the first three days of life was associated with lower 90 day survival in extremely preterm infants. SGA infants had enhanced vulnerability to lower oxygen saturation targets as evidenced by lower achieved oxygen saturation and an association between increased IH events and lower survival.

Keywords

Hypoxia; small for gestational age; supplemental oxygen; oxygen saturation; intermittent hypoxemia

Controversy persists in the optimal oxygen saturation range in preterm infants. A series of large collaborative multicenter trials, randomizing preterm infants of <28 weeks gestation to a lower (85–89%) versus higher (91–95%) oxygen saturation target, documented a decrease in the incidence of severe retinopathy of prematurity with an unexpected increase in mortality in the lower target group^{1, 2}. Due to these emerging data, some clinicians are avoiding an oxygen saturation target of 85 to 89% even though the reason for the increase in mortality is currently unknown.

We and others have shown an association between an increased incidence of intermittent hypoxemia (IH) during early postnatal life and morbidity^{3, 4}. In addition, we have shown a higher number of IH events in a subcohort of infants enrolled in the Surfactant, Positive Pressure and Oxygen Trial (SUPPORT)¹ who were randomized to the lower versus higher oxygen saturation target⁵. Furthermore, in the entire SUPPORT infant cohort, we have most recently shown that small for gestational age (SGA) infants had a higher mortality than appropriate for gestational age (AGA) infants with the highest mortality seen in the SGA infants randomized to the lower oxygen saturation target⁶. Therefore, being SGA, having a lower oxygen saturation level, and a high incidence of IH events may be a synergistic combination that increases the risk of death in extremely preterm infants. Previous analyses of SUPPORT data were conducted by an intention to treat analysis. However, the challenge of keeping the infants within each target resulted in overlap of median oxygen saturation levels between the lower and higher target groups. Therefore, the purpose of this study was twofold: to characterize actual achieved patterns of oxygenation in AGA versus SGA infants enrolled in SUPPORT and randomized to a higher versus lower oxygen saturation target and the association between actual achieved oxygen saturation levels during the first 72 hours of life and survival in AGA and SGA infants.

Methods

This study included 1316 preterm infants of 24 to 27 6/7 weeks gestation who were enrolled in SUPPORT¹, a randomized trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00233324): NCT00233324) to compare the target ranges of 85–89% (lower) or 91–95% (higher) oxygen saturation on the composite outcome of severe retinopathy of prematurity, death before hospital discharge or both. In the main trial 654 infants were randomized to the lower target while 662 infants were randomized to the higher target. 41/654 in the lower and 55/662 infants in the higher target were small for gestational age (SGA), defined as <10% on the Alexander curves⁷. Gestational age was based on last menstrual period, obstetrical variables and prenatal ultrasound and/or physical criteria, neurological exam, combined physical and gestational age exam or examination of

the lens. Infants were randomized by two hours after birth to the specified target until 36 weeks of postmenstrual age or until the infant no longer required supplemental oxygen and ventilator or CPAP for more than 72 hours, whichever came first. During this period oxygen saturation data were continuously sampled every 10 sec (.1Hz) with an oximeter averaging time of 16 sec (Masimo, Radical, Yorba, CA). At two sites higher resolution data were collected in 128 infants with one sample every 2 sec (.5Hz) and an averaging time of 2 sec. Data from these two sites were downsampled to one sample every 10 sec to allow for similar sampling resolution among sites. IRB approval and parental consent was obtained for the main SUPPORT trial with additional IRB approval for the current study.

Oxygen saturation waveform patterns were quantified using previously validated custom software (Matlab, Natick, MA)⁸. Waveform files were initially screened for data integrity including missing data, valid dates, and spurious noise artifact. Noise artifact included flat line of signals and values of zero for either heart rate or oxygen saturation. Infants with valid oxygen saturation data who survived until 3 days of age were included in this study. 1054 infants had oxygen saturation data of acceptable integrity for analysis (58 infants died and 204 infants had unacceptable quality or missing data within the first 3 days of life). In infants who died, the last day before death was removed to avoid bias in oxygen saturation patterns due to deterioration in that interval.

During the main trial, infants were placed on electronically modified oximeters to maintain blinding of the oxygen saturation target randomization. The oximeters were altered to display 88–92% when infants were in the randomized target but were offset by $\pm 3\%$ in this range and returned to true values below 84% and above 96%. Altered oxygen saturation readings were adjusted back to the actual original oxygen saturation values. As previously described, quadratic interpolation was used to estimate the distribution in transition areas where there was a lack of one-to-one matching⁹. Oxygen saturation data were sampled at .1Hz, or 1 sample every 10 sec. Based on the Nyquist sampling theorem, detection of intermittent hypoxemia (IH) events was limited to events ≤ 20 seconds in duration ($2 \times$ the sample period). Intermittent hypoxemia events were thus defined as a fall in oxygen saturation $< 80\%$ for ≤ 20 sec and ≤ 5 min in duration to distinguish IH events from sustained hypoxemia. Previous findings in infants enrolled in the Canadian Oxygen Trial⁴ have shown a relationship between IH events and morbidity that was limited to events of > 1 minute in duration. Therefore, separate analyses were performed for “shorter” IH of 20sec to 1 minute and “longer” IH of 1–5 minutes in duration. Median oxygen saturation and IH patterns were summarized over daily intervals.

Statistical Analyses

Daily achieved oxygen saturation patterns were graphically displayed across the first month of life among SGA and AGA infants within each oxygen saturation target group (Figure 1; available at www.jpeds.com). However, comparison of achieved oxygen saturation between SGA/AGA infants within each randomization target group was limited to the first 3 days of life, while $> 90\%$ of infants were still alive, to avoid the potential bias due to the decline in survival resulting from an increased and disproportionate incidence of early death in the SGA group relative to the AGA group. During the first 3 days of life, comparisons were

made between groups using a generalized linear model (GLIMMIX procedure) to account for correlation within multiple births.

We then sought to assess the association between oxygen saturation and growth status at birth on the outcome of death within 90 days after birth. All infants in both target groups were combined, and actual achieved oxygenation patterns were then stratified by SGA/AGA and quartiles. The bottom quartile of achieved median oxygen saturation was compared with the combined upper three quartiles, and the top quartile for percent time with hypoxemia (<80%) and IH was compared with the combined lower three quartiles. Demographic and clinical factors potentially associated with 90 day survival were determined using both Kaplan-Meier method and the Cox proportional hazard model (Table I). The association of the first 3-day achieved oxygenation patterns on 90-day survival between SGA and AGA infants was evaluated using survival analysis. Probability of 90-day survival and survival curves by SGA/AGA and each saturation variable category were explored using the Kaplan-Meier method while relative hazard ratios of early death were calculated using Cox proportional hazard models. Infants from multiple births were included in this study with correlation within multiple births being considered in the generalized linear mixed model (GLIMMIX procedure, SAS, Inc, NC) and Cox proportional hazard models. All data analyses were performed using SAS version 9.4 (SAS Inc, NC) with a two-sided p value of $p < 0.05$ considered as statistically significant.

Results

Infants were enrolled from February 2005 through February 2009. A lower 90 day survival rate was associated with lower birthweight ($p < 0.0001$) and younger gestational age ($p < 0.0001$) (Table I).

Association of SGA vs AGA status and oxygenation patterns in the higher and lower oxygen saturation target groups

Our previous study revealed the highest mortality in SGA infants randomized to the lower oxygen saturation target based on intention to treat design⁶. Because of the large overlap in true oxygen saturation levels between target groups, we sought to examine actual achieved patterns of oxygenation in AGA and SGA infants in the lower and higher target groups during the first 3 days of life. (Extended daily alterations in oxygen saturation patterns and dropout rates over the first 28 days of life are presented in Figure 1).

Median Oxygen Saturation—AGA infants in the higher target had the highest median oxygen saturation compared with both SGA and AGA infants in the lower target (both $p < 0.0001$) and SGA infants in the higher target ($p = .012$) during the first 3 days of life (Table II). In contrast, SGA infants in the lower target maintained a significantly lower median oxygen saturation compared with all other infant groups (all $p < 0.0001$). The difference between the higher and lower target was significantly larger in the SGA versus AGA infants (2.8 vs 1.6%, p interaction=0.02).

Time with Hypoxemia—During the first 3 days of life there was no difference in the time spent with hypoxemia (<80%) between AGA and SGA infants in the higher target (Table II).

In contrast, AGA and SGA infants in the lower target spent a significantly higher percent time with hypoxemia compared with both AGA and SGA infants in the higher oxygen saturation target (Table II). SGA infants in the lower target had the highest amount of time with hypoxemia ($4.6 \pm 0.5\%$) compared with all infants groups including AGA infants within the same oxygen saturation target ($p=0.0038$) (Table II). The difference between the high and low target was comparable in the SGA versus AGA infants (2.4 vs 1.3%, p interaction=0.11) (Table II).

Intermittent Hypoxemia—Separate analyses were performed for “shorter” IH of 20sec to 1 minute and “longer” IH of 1–5 minutes in duration (Table II). There were no differences in the incidence of shorter or longer IH between SGA and AGA infants within the higher target. AGA infants in the lower target group had a greater incidence of both shorter and longer IH events compared with AGA infants in the higher target during the first 3 days of life (both $p<0.0001$, Table II). The lower target SGA infants had the greatest incidence of longer IH events compared with all other infant groups (all $p<0.0001$). However, there was no significant difference in the incidence of shorter IH events between SGA and AGA infants in the lower target. The difference between the high and low target was significantly larger in the SGA versus AGA infants for longer IH events (9.9 vs 4.4 IH/day, interaction $p=0.006$) with no statistically significant difference in shorter IH events (7.5 vs 5.2, IH/day, interaction $p=0.34$).

Association of oxygenation patterns with survival in SGA versus AGA infants

Based on the analysis above, we hypothesized that non-survival would be associated with being SGA, having a lower median oxygen saturation and a higher incidence of longer IH events. Kaplan Meier survival curves based on oxygen saturation variables are presented in Figure 2.

Median Oxygen Saturation—Median oxygen saturation was calculated for all infants then divided into quartiles. The lowest quartile for oxygen saturation ($<92\%$) was compared with the combined additional three quartiles ($>92\%$) and stratified by SGA/AGA (Figure 2, A). AGA infants with a median oxygen saturation $>92\%$ had the highest 90 day survival rate of 90.8% with no statistically significant difference in survival between SGA and AGA infants in this oxygen saturation range (HR 1.8; 95% CI, .8–4.0, $p=0.1291$, Table III). In contrast, there was a lower 90 day survival in both AGA (HR 1.9; 95% CI, 1.2–2.8, $p=0.0013$) and SGA (HR 6.1; 95% CI, 3.5–10.4, $p<0.0001$) infants in the lowest quartile ($<92\%$) when compared with AGA infants $>92\%$. Although the SGA infants $<92\%$ had a lower survival of 54.3%, the difference in survival status between SGA infants $<92\%$ and $>92\%$ versus AGA infants $<92\%$ and $>92\%$ was not statistically different (interaction, $p=0.2542$).

Time with Hypoxemia—Hazard ratios were calculated for quartile levels of percent time with hypoxemia. The top quartile of infants, $>3.2\%$ time with hypoxemia, was compared with infants who spent $<3.2\%$ time with hypoxemia (Figure 2, B). There was no association between the overall time with hypoxemia and survival in the AGA infant groups (HR 0.98; 95% CI, .6–1.5, $p=0.9218$, Table III). In infant groups with the lowest amount of time with

hypoxemia (<3.2% time), SGA infants had an increased risk of death compared with AGA infants (HR 2.3; 95% CI, 1.3–4.3, $p<0.0077$). SGA infants with >3.2% time with hypoxemia were at greater risk for death (HR 3.9; 95% CI, 2.1–7.2, vs AGA <3.2% time with hypoxemia, $p<0.0001$) with the lowest 90 day survival of 60.7% (interaction, $p=0.2539$).

Intermittent Hypoxemia—Because previous data from the Canadian Oxygen Trial showed a relationship between IH events and morbidity that was limited to IH events more than a minute in duration⁴ two separate analyses were performed for shorter IH (20sec–1min) (highest quartile; 14.7 events/day) and longer IH (1–5 min) (highest quartile; 12 events/day) events (Figure 2, C and D). A higher incidence of either longer or shorter IH events, as measured by the highest quartiles, was not associated with increased death in AGA infants (Table III). In contrast, the largest hazard ratios were seen in the SGA infants in the highest quartiles for both shorter IH (HR 6.1; 95% CI, 3.2–11.8, $p<0.0001$, interaction $p=0.0255$) and longer IH (HR 3.6; 95% CI, 2.0–6.3, $p<0.0001$, interaction $p=0.1747$) with the lowest survival of 47.4% in SGA infants who had >14.7 shorter IH events per day.

Discussion

Previous data from the SUPPORT multicenter trial randomizing infants to a lower (85–89%) versus higher (91–95%) saturation target revealed a higher mortality in the lower oxygen saturation target group. We have previously found evidence of an interaction between SGA infants and lower oxygen targets associated with increased mortality based on an intention to treat analysis⁶. The objective of this analysis was to characterize actual achieved patterns of oxygenation in AGA versus SGA infants enrolled in SUPPORT and randomized to a higher versus lower oxygen saturation target and the association between actual achieved oxygen saturation levels and survival in AGA and SGA infants. This study found that SGA infants in the lower target group had the lowest achieved oxygen saturation levels and highest incidence of longer IH during the first three days of life compared with lower target AGA infants and both higher target SGA and AGA infants. In addition, we observed that being in the lowest quartile for median oxygen saturation during the first three days of life was associated with decreased infant survival at 90 days for both AGA and SGA infants, with SGA infants with the lowest quartile oxygen saturation having a particularly low survival of 54.3%. Furthermore, both time with hypoxemia and incidence of IH events were significantly associated with lower survival only in the SGA infants.

The mechanisms by which achieved oxygenation appears to be compromised (2.2% lower) in SGA infants assigned to the lower oxygen saturation target have yet to be elucidated. Possible contributors include impaired pulmonary vascular growth and/or pulmonary vasoconstriction¹⁰. Lamb models of intrauterine growth restriction have demonstrated postnatal suppression of the ventilatory response to acute hypoxia¹¹ and both structural and functional immaturity of the lungs¹² during early postnatal life. These factors may have resulted in a lower respiratory reserve in SGA versus AGA infants due to impaired lung development resulting in a higher probability for desaturation when alveolar PO_2 is lower. Our study revealed a greater percentage of time with hypoxemia and a higher incidence of long IH events in AGA infants in the lower versus higher target, similar to previous data by Di Fiore et al⁵ and consistent with McEvoy et al¹³ showing a relationship between O_2 levels

and intermittent hypoxemia in former preterm infants with chronic lung disease. The increased incidence of IH events and time with hypoxemia may be due to a lower baseline alveolar PO₂ in the lower target which, in a model based analysis, has been shown to cause an early onset of desaturation¹⁴. The SEM's were much larger in the SGA compared with AGA infants. This may reflect a possible correlation between growth status and variability in oxygen saturation or may be a manifestation of a much larger sample size in the AGA infant cohort. Although it may not be surprising that the lower target was associated with an increase in IH events in both the SGA and AGA infants, a higher incidence of IH events associated with decreased survival was only seen in the SGA infants.

Following the results of the recent multicenter trials showing an increased mortality in infants randomized to the lower oxygen saturation target of 85–89%^{1,2} editorials have recommended a move towards a higher oxygen saturation target range of 90–95%^{15, 16}. Although the optimal specific range of oxygen saturations for infant survival has yet to be determined, this study has shown that a median oxygen saturation of 92% during the first three days of life may influence infant survival. The oxygen saturation quartiles in this study may simply reflect illness severity as opposed to a specific oxygen saturation range associated with survival and may be one possible explanation for differences in mortality outcomes between the SUPPORT and Canadian Oxygen Trial (COT)¹⁷. The SUPPORT enrollment protocol had no study exclusions after delivery. In contrast, COT enrollment occurred in the first 18 hours with exclusion criteria resulting in the most unstable infants being excluded from the study. We speculate that greater illness severity may have contributed to enhanced vulnerability to low achieved oxygen saturation in SUPPORT versus COT cohorts. Given the limitation of additional potential illness severity contributors that may have played a role in survival during the first 72 hours of life, these results suggest that in preterm infants, and especially SGA infants, survival may be improved by targeting the upper range of this oxygen saturation target during the first few days of life. The potential benefit of a higher median oxygen saturation on survival must be balanced with the increased risk of morbidities associated with hyperoxia exposure such as ROP.

Intermittent hypoxic episodes are almost universal in extremely low birth weight infants of <1 kg birth weight and frequently go undocumented by the clinical staff¹⁸. They are typically a consequence of impaired respiratory control and may occur in spontaneously breathing or ventilated preterm infants^{3, 19, 20}. Intermittent hypoxia and/or related apnea events during early postnatal life have been linked to neurodevelopmental impairment^{21, 22, 23, 24}, attention deficit disorder²⁵, neurotransmitter imbalance²⁵, retinopathy of prematurity^{3, 26}, cardiovascular regulation²⁷ and growth restriction²⁷ in both human infants and neonatal animal models. We are only beginning to appreciate that patterns of IH may play a role in both detrimental and beneficial effects on the respiratory, cardiovascular, and nervous systems among others^{26, 28}. For example, both human and rodent neonatal models suggest that clustering of IH events can lead to increased neovascularization associated with severe ROP^{8, 29}. Recent data from the Canadian Oxygen Trial (COT) have shown an association between IH events and motor/cognitive impairment, language delay and severe ROP that was limited to IH events of 1 minute in duration⁴. In contrast to COT, our observation between IH events and survival in the SGA cohort was not limited to longer IH events suggesting that a high incidence of IH events of even 20 sec in

duration during early postnatal life may put SGA infants at risk of death during the first 3 months of life. Due to the nature of survival analysis and the high dropout rate due to death during the first week of life we cannot address the detriments of such events on mortality beyond the first few days of life.

It is well known that SGA infants have a lower survival compared with AGA infants^{30, 31}. The largest proportion of SGA infant mortality has been reported to occur during the first 12 hours of life³⁰. Inclusion in the current study relied on the presence of at least three days of oxygen saturation waveform data and, correspondingly, survival of at least three days duration. Therefore, this study may represent relatively more stable infants in the SGA spectrum. Never-the-less, intra-uterine growth restriction has demonstrated lasting effects on lung structure and function including decreased pulmonary alveolar and vessel growth and pulmonary arterial endothelial cell dysfunction in a sheep model³² in addition to a predisposition to BPD³¹ and pulmonary hypertension³³ in human neonates. SGA infants had a comparable number of IH <1min when compared with AGA infants (Figure 1) yet, in contrast to AGA infants, survival of SGA was highly associated with the incidence of both long and short IH events. Therefore, the risk factors associated with intrauterine growth restriction combined with a future hit of either sustained and/or intermittent hypoxia during a vulnerable transition period during the first few days of life may have provided a lethal interaction resulting in increased mortality in this fragile infant cohort.

Analyses were not adjusted for potential confounding factors (ie asphyxia at birth, ventilator treatment, hypoglycemia etc) as it was unclear what factors were additional contributory factors as opposed to causal as a result of being SGA. We also acknowledge that many comparisons were performed thus inflating the possibility of a type I error. Lastly, 204 infants were not included in the analysis due to missing or unacceptable quality of data during the first 3 days of life. As these cases occurred at random we do not anticipate that this would cause a selection bias between infant groups.

The results of this study suggests that the optimal achieved oxygen saturation during the first few days of life to improve survival in preterm infants, and especially SGA infants, may be an oxygen saturation >92%. The application of such a paradigm in clinical practice may be unrealistic given the multitude of studies showing the challenge of keeping infants within any given target regardless of the use of manual or automated adjustments in supplemental oxygen^{34, 35}. The results of this study may be a reflection of the move towards oxygen saturation monitoring and away from transcutaneous PO₂ monitoring whereby, even infants in the higher saturation target of 90–95% often have PaO₂ levels well below the recommended published guidelines³⁶.

In summary, this study found that SGA infants in the lower target group had the lowest median oxygen saturation and highest incidence of longer IH during the first three days of life compared with lower target AGA infants and both higher target SGA and AGA infants. In addition, this study found an association between median oxygen saturation during the first three days of life and infant survival at 90 days in both AGA and SGA infants. In contrast, the association between time with hypoxemia and incidence of IH events with decreased survival was limited to the SGA infants. Therefore, maintaining extremely low

gestational age infants, and especially SGA infants, in the higher end of recommended guidelines during the first few days of life may improve infant survival.

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Appendix

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Abbreviations

SGA	Small for gestational age
AGA	Appropriate for gestational age
IH	Intermittent hypoxemia
SUPPORT	Surfactant, Positive Pressure and Oxygen Trial

References

1. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010; 362:1959–1969. [PubMed: 20472937]
2. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med*. 2011; 364:1680–1682. [PubMed: 21524227]
3. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr*. 2010; 157:69–73. [PubMed: 20304417]
4. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. *JAMA*. 2015; 314:595–603. [PubMed: 26262797]
5. Di Fiore JM, Walsh M, Wrage L, Rich W, Finer N, Carlo WA, et al. Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia. *J Pediatr*. 2012; 161:1047–1052. [PubMed: 22738947]
6. Walsh MC, Di Fiore JM, Martin RJ, Gantz M, Carlo WA, Finer N. Association of Oxygen Target and Growth Status With Increased Mortality in Small for Gestational Age Infants: Further Analysis of the Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial. *JAMA Pediatr*. 2016; 170:292–294. [PubMed: 26746140]
7. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996; 87:163–168. [PubMed: 8559516]
8. Di Fiore JM, Kaffashi F, Loparo K, Sattar A, Schluchter M, Foglyano R, et al. The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants. *Pediatr Res*. 2012; 72:606–612. [PubMed: 23037873]

9. Boost II United Kingdom Collaborative Group, Boost II Australia Collaborative Group, Boost II New Zealand Collaborative Group. Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med.* 2013; 368:2094–2104. [PubMed: 23642047]
10. Mourani, PMAS. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. In: Kallapur, SGPG., editor. *Clinics in perinatology Bronchopulmonary dysplasia: An update.* Elsevier; Philadelphia: 2015. p. 839-855.
11. Moss TJ, Davey MG, McCrabb GJ, Harding R. Development of ventilatory responsiveness to progressive hypoxia and hypercapnia in low-birth-weight lambs. *J Appl Physiol* (1985). 1996; 81:1555–1561. [PubMed: 8904568]
12. Harding R, Tester ML, Moss TJ, Davey MG, Louey S, Joyce B, et al. Effects of intra-uterine growth restriction on the control of breathing and lung development after birth. *Clin Exp Pharmacol Physiol.* 2000; 27:114–119. [PubMed: 10696539]
13. McEvoy C, Durand M, Hewlett V. Episodes of spontaneous desaturations in infants with chronic lung disease at two different levels of oxygenation. *Pediatr Pulmonol.* 1993; 15:140–144. [PubMed: 8327275]
14. Sands SA, Edwards BA, Kelly VJ, Skuza EM, Davidson MR, Wilkinson MH, et al. Mechanism underlying accelerated arterial oxygen desaturation during recurrent apnea. *Am J Respir Crit Care Med.* 2010; 182:961–969. [PubMed: 20522790]
15. Bancalari E, Claure N. Oxygenation targets and outcomes in premature infants. *JAMA.* 2013; 309:2161–2162. [PubMed: 23645072]
16. Polin RA, Bateman D. Oxygen-saturation targets in preterm infants. *N Engl J Med.* 2013; 368:2141–2142. [PubMed: 23642082]
17. Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA.* 2013; 309:2111–2120. [PubMed: 23644995]
18. Brockmann PE, Wiechers C, Pantalitschka T, Diebold J, Vagedes J, Poets CF. Under-recognition of alarms in a neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed.* 2013; 98:F524–527. [PubMed: 23716498]
19. Dimaguila MA, Di Fiore JM, Martin RJ, Miller MJ. Characteristics of hypoxemic episodes in very low birth weight infants on ventilatory support. *J Pediatr.* 1997; 130:577–583. [PubMed: 9108856]
20. Barrington KJ, Tan K, Rich W. Apnea at discharge and gastro-esophageal reflux in the preterm infant. *J Perinatol.* 2002; 22:8–11. [PubMed: 11840235]
21. Pillekamp F, Hermann C, Keller T, von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity – implications for neurodevelopment. *Neonatology.* 2007; 91:155–161. [PubMed: 17377399]
22. Janvier A, Khairy M, Kokkoti A, Cormier C, Messmer D, Barrington KJ. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *J Perinatol.* 2004; 24:763–768. [PubMed: 15329741]
23. Taylor HG, Klein N, Schatschneider C, Hack M. Predictors of early school age outcomes in very low birth weight children. *J Dev Behav Pediatr.* 1998; 19:235–243. [PubMed: 9717132]
24. Ratner V, Kishkurno SV, Slinko SK, Sosunov SA, Sosunov AA, Polin RA, et al. The contribution of intermittent hypoxemia to late neurological handicap in mice with hyperoxia-induced lung injury. *Neonatology.* 2007; 92:50–58. [PubMed: 17596736]
25. Decker MJ, Hue GE, Caudle WM, Miller GW, Keating GL, Rye DB. Episodic neonatal hypoxia evokes executive dysfunction and regionally specific alterations in markers of dopamine signaling. *Neuroscience.* 2003; 117:417–425. [PubMed: 12614682]
26. Penn JS, Henry MM, Wall PT, Tolman BL. The range of PaO₂ variation determines the severity of oxygen-induced retinopathy in newborn rats. *Invest Ophthalmol Vis Sci.* 1995; 36:2063–2070. [PubMed: 7657545]
27. Pozo ME, Cave A, Koroglu OA, Litvin DG, Martin RJ, Di Fiore J, et al. Effect of postnatal intermittent hypoxia on growth and cardiovascular regulation of rat pups. *Neonatology.* 2012; 102:107–113. [PubMed: 22677790]

28. Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. *Am J Physiol Regul Integr Comp Physiol*. 2014; 307:R1181–1197. [PubMed: 25231353]
29. Coleman RJ, Beharry KD, Brock RS, Abad-Santos P, Abad-Santos M, Modanlou HD. Effects of brief, clustered versus dispersed hypoxic episodes on systemic and ocular growth factors in a rat model of oxygen-induced retinopathy. *Pediatr Res*. 2008; 64:50–55. [PubMed: 18344903]
30. Griffin JJ, Lee HC, Profit J, Tancedi DJ. The smallest of the small: short-term outcomes of profoundly growth restricted and profoundly low birth weight preterm infants. *J Perinatol*. 2015; 35:503–510. [PubMed: 25590218]
31. Zeitlin J, El Ayoubi M, Jarreau PH, Draper ES, Blondel B, Kunzel W, et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. *J Pediatr*. 2010; 157:733–739 e731. [PubMed: 20955846]
32. Rozance PJ, Seedorf GJ, Brown A, Roe G, O'Meara MC, Gien J, et al. Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep. *Am J Physiol Lung Cell Mol Physiol*. 2011; 301:L860–871. [PubMed: 21873446]
33. Check J, Gotteiner N, Liu X, Su E, Porta N, Steinhorn R, et al. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. *J Perinatol*. 2013; 33:553–557. [PubMed: 23328924]
34. Claure N, Bancalari E. Automated respiratory support in newborn infants. *Semin Fetal Neonatal Med*. 2009; 14:35–41. [PubMed: 18829405]
35. van Kaam AH, Hummler HD, Wilinska M, Swietlinski J, Lal MK, te Pas AB, et al. Automated versus Manual Oxygen Control with Different Saturation Targets and Modes of Respiratory Support in Preterm Infants. *J Pediatr*. 2015; 167:545–550. e541–542. [PubMed: 26144575]
36. Quine D, Stenson BJ. Arterial oxygen tension (Pao₂) values in infants <29 weeks of gestation at currently targeted saturations. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94:F51–53. [PubMed: 18285372]

Figure 1.

online. Daily Patterns of oxygenation during the first month of life in AGA and SGA infants enrolled in SUPPORT and randomized to lower (85–89%) or higher (91–95%) oxygen saturation targets including A) Median oxygen saturation, B) Time with hypoxemia (<80%), C) shorter intermittent hypoxemia events (IH) of 20s–1min and D) longer IH of 1–5min. (mean $\pm$ SEM)

Figure 2.

Kaplan Meier survival analysis in AGA and SGA infants based on actual achieved patterns of oxygenation during the first three days of life. Group stratifications were based on quartile cutoffs with the lowest quartile compared with all others for median oxygen saturation and the highest quartile compared with all others for time <80% and frequency of IH events. A) Median oxygen saturation, B) % time with hypoxemia (<80%) C) Short IH events of 20sec to 1 minute in duration and D) Long IH events of 1 to 5 minutes in duration.

Table 1

Patient Demographics

Factor	Overall No. (%)	Alive at 90 days No. (%)	P value
Overall	1054	921 (87.4)	
Sex			
Female	495 (47)	442 (89.3)	0.10
Male	559 (53)	479 (85.7)	
Race			
Black	403 (38.2)	354 (87.8)	0.57
White	418 (39.7)	368 (88)	
Other	233 (22.1)	199 (85.4)	
Target group			
Higher	533 (50.6)	473 (88.7)	0.18
Lower	521 (49.4)	448 (86)	
SGA			
No	977 (92.7)	867 (88.7)	<0.0001
Yes	77 (7.3)	54 (70.1)	
Multiple birth			
No	798 (75.7)	704 (88.2)	0.15
Yes	256 (24.3)	217 (84.8)	
Early sepsis			
No	1024 (97.2)	895 (87.4)	0.91
Yes	30 (2.8)	26 (86.7)	
Birth weight quartile			
360 to 690	264 (25)	209 (79.2)	<0.0001
691 to 815	268 (25.4)	236 (88.1)	
820 to 967	257 (24.4)	224 (87.2)	
969 to 1590	265 (25.1)	252 (95.1)	
GA at birth quartile			
24 to 25.1	271 (25.7)	206 (76)	<0.0001
25.3 to 26.1	275 (26.1)	242 (88)	
26.3 to 27.1	220 (20.9)	203 (92.3)	
27.1 to 28	288 (27.3)	270 (93.8)	

Table 2

Patterns of oxygenation in AGA and SGA infants randomized to a lower versus higher oxygen saturation target

(LS-mean±SEM)	First 3 Days of Life	p value		
Median SpO ₂ (%)		vs Higher Target:AGA	vs Higher Target:SGA	vs Lower Target:AGA
Higher Target: AGA	94.6 ± 0.1			
Higher Target: SGA	93.6 ± 0.4	0.012		
Lower Target: AGA	93.0 ± 0.1	<0.0001	0.083	
Lower Target: SGA	90.8 ± 0.4	<0.0001	<0.0001	<0.0001
P (interaction)		0.02		
Time <80% (%)				
Higher Target: AGA	1.8 ± 0.1			
Higher Target: SGA	2.2 ± 0.4	0.367		
Lower Target: AGA	3.1 ± 0.1	<0.0001	0.0365	
Lower Target: SGA	4.6 ± 0.5	<0.0001	0.0003	0.0038
P (interaction)		0.11		
Shorter IH (no./day)				
Higher Target: AGA	8.0 ± 0.5			
Higher Target: SGA	8.6 ± 1.5	0.726		
Lower Target: AGA	13.3 ± 0.5	<0.0001	0.0031	
Lower Target: SGA	16.0 ± 1.7	<0.0001	0.0012	0.1135
P (interaction)		0.34		
Longer IH (no./day)				
Higher Target: AGA	6.3 ± 0.4			
Higher Target: SGA	8.0 ± 1.3	0.205		
Lower Target: AGA	10.7 ± 0.4	<0.0001	0.0386	
Lower Target: SGA	17.9 ± 1.4	<0.0001	<0.0001	<0.0001
P (interaction)		0.006		

Intermittent Hypoxemia (IH); Shorter IH, 20sec–1min; Longer IH, 1–5min

Table 3
Patterns of Oxygenation during the First Three Days of Life as a Predictor of Mortality at 90 days

		No. of Infants	90 Day Survival	HR (95% CI)	P Value [‡]
Median SpO ₂					
	AGA >92%	715	90.8	1	
	SGA >92%	42	83.3	1.8 (.8, 4.0)	0.1291
	AGA 92%	262	83.2	1.9 (1.2, 2.8)	0.0013
	SGA 92%	35	54.3	6.1 (3.5, 10.4)	<.0001
	P (interaction)				0.2541
Time <80%					
	AGA <3.2%	742	88.7	1	
	SGA <3.2%	49	75.5	2.3 (1.3, 4.3)	0.0077
	AGA 3.2%	235	88.9	0.98 (.6, 1.5)	0.9218
	SGA 3.2%	28	60.7	3.9 (2.1, 7.2)	<.0001
	P (interaction)				0.2543
Short IH [*]					
	AGA <14.7/day	733	88.8	1	
	SGA <14.7/day	58	77.6	2.1 (1.2, 3.7)	0.0142
	AGA 14.7/day	244	88.5	1.0 (.6, 1.6)	0.8994
	SGA 14.7/day	19	47.4	6.1 (3.2, 11.8)	<.0001
	P (interaction)				0.0255
Long IH [*]					
	AGA <12/day	745	88.3	1	
	SGA <12/day	46	76.1	2.2 (1.2, 4.3)	0.0162
	AGA 12/day	232	90.1	0.8 (.5, 1.3)	0.4549
	SGA 12/day	31	61.3	3.6 (2.0, 6.3)	<.0001
	P (interaction)				0.1747

^{*} Short: 20sec–1min, Long: 1–5min

[‡] vs Highest Median SpO₂ quartile (AGA>92%) or lowest quartile for time <80% (AGA<3.2%), short IH (AGA<14.7/day) and long IH (AGA <12/day)

There were no statistically significant differences in gestational age, race, gender, multiple births, or early sepsis between infant groups. Therefore, unadjusted hazard ratios are presented.