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Neonatal Oxygen Saturations and Blood Pressure at School-Age in Children Born Extremely Preterm: A Cohort Study

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Abstract

Objective: To explore the relationship between neonatal oxygen saturation and BP at age 6-7 years in a cohort of infants born extremely preterm.

Study Design: Infants <28 weeks gestation were assigned to a higher or lower oxygen saturation target. Oximeter data were monitored throughout the neonatal period. A subset of survivors was seen at age 6. BP was measured and compared by group assignment, achieved saturations, and time spent in hypoxemia (saturations < 80%).

Results: There was no difference in systolic or diastolic BP between assigned groups. Median achieved weekly oxygen saturation was not associated with BP. Longer duration of hypoxemia during the first week of age was associated with higher systolic BP.

Conclusion: Neither target nor actual median oxygen saturations in this study was associated with BP at school age. Increased duration of hypoxemia in the first postnatal week was associated with higher systolic BP at 6-7 years of age.

Keywords

preterm; blood pressure; school age; hypertension; oxygen saturation; hypoxia

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Disclosures

None

Introduction

With the steady decrease in mortality among infants born extremely preterm over the decades, concerns have been raised about future cardiovascular health in survivors.(1) Infants born preterm are at higher risk than those born at term for elevated blood pressure (BP), decreased glucose tolerance and increased low-density lipoprotein in adulthood, all of which contribute significantly to cardiovascular risk.(2-4)

Prematurity is associated with elevated BP from infancy into adulthood.(2,5,6) A recent meta-analysis showed that elevated BP occurred more frequently in young adults born very low birth weight (VLBW) than in term counterparts, with an increase of 3.4mmHg (95% confidence interval (CI), 2.2-4.6) and 2.1mmHg (95% CI, 1.3-3.0) in systolic and diastolic BP, respectively.(2) Those differences may be significant, as increases in BP trajectories as small as 2mmHg throughout young adulthood are linked to the development of atherosclerosis in middle-age.(7)

The cause of this association is not well understood. Exposure to hypoxemia may play a role, as animal studies have shown that chronic hypoxemia in the neonatal period results in elevated systolic BP that persists into adulthood.(8,9) Healthy children and adults who experience chronic hypoxemia from living at higher altitude are at increased risk of pre-hypertension and hypertension over individuals living at sea-level.(10,11) Additionally, children with obstructive sleep apnea (OSA), which results in chronic intermittent hypoxemia, have higher systolic and diastolic BP compared to controls.(12)

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)(13) randomized 1316 extremely preterm infants to higher (91-95%) or lower (85-89%) oxygen saturation target groups to evaluate the combined outcome of retinopathy of prematurity (ROP) or death. Infants in that study had oxygen saturation (SpO_2) data recorded once every 10 seconds from birth until 36 weeks corrected gestational age (GA), or until the infant was breathing room air for 3 days. A sub-cohort of those children was enrolled in the Neuroimaging and Neurodevelopmental Outcomes study (NEURO), therefore had detailed neonatal neuroimaging, and neurodevelopmental and anthropometric follow-up at age 6, which included assessment of BP. These data allowed us to explore the association of early oxygen saturation and BP at school age, and to test the hypothesis that assignment to a lower oxygen saturation target group or lower achieved oxygen saturations in the neonatal period may be associated with elevated BP at follow-up.

Methods

This is a cohort analysis of a subgroup of children enrolled in the secondary study SUPPORT Neuroimaging and Neurodevelopmental Outcomes school-age cohort (NEURO) (14) conducted by the National Institute for Child Health and Human Development (NICHD) Neonatal Research Network (NRN). The study was approved by Institutional Review Boards at all study sites. Infants at 16 NRN sites were enrolled between February 2005 and February 2009 after informed parental consent was obtained. This sub-cohort was originally enrolled in the SUPPORT trial, which randomized infants born between 24 weeks

0 days and 27 weeks 6 days to a lower (85-89%) or higher (91-95%) oxygen saturation target. Infants were started on their assigned target range within 2 hours after birth and remained in their assigned group until 36 weeks corrected GA or until the infant did not require supplemental O_2 or positive pressure ventilation for more than 72 hours, whichever occurred first. Masked pulse oximeter data (Masimo Corp, Irvine, California) were recorded every 10 seconds during the study period.

Children enrolled in the NEURO sub-cohort had additional neuroimaging including near-term or term equivalent MRI during the neonatal period, therefore it is a select subgroup of the SUPPORT cohort. Survivors had comprehensive neurodevelopmental evaluation done at 6 – 7 years of age. Separate informed consent was obtained for this follow-up. Weight, height, and BP were measured at this visit to determine the incidence of elevated BP, hypertension and associated risk factors. BP measurements were taken by investigators blinded to study group assignment, following techniques recommended by the Fourth Task Force on Blood Pressure Control for Children(15). The children sat in a quiet room with the right arm fully exposed and resting on a supportive surface at heart level. The American Diagnostic Corporation ADC E Sphygmomanometer was used to accurately, non-invasively and automatically measure systolic and diastolic BP and pulse rate. The girth of the right arm was measured to determine appropriate cuff size, covering approximately 75% of the upper arm. BP was taken twice, two minutes apart. If the systolic or diastolic BP was greater or equal to the 90^{th} percentile by the automatic method, it was repeated manually with auscultation.

For this analysis, we used the definitions of high BP and hypertension for children between 1 and 13 years of age from the “Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents”(16) in which high BP is defined as averaged systolic or diastolic BP between the 90^{th} and 95^{th} percentiles or systolic BP between 120 – 129 mmHg with a diastolic BP < 80 mmHg (whichever is lower) and hypertension is defined as systolic or diastolic BP ≥ 95^{th} percentile or ≥ 130/80 mmHg.

The measurements of systolic and diastolic BP were averaged and percentiles for each were determined based on age, sex and height. The hypothesis that lower oxygen saturation would correlate with higher BP was tested by two different approaches: (1) exploring the association between assigned O_2 saturation target group and BPs at school-age, and (2) analyzing the correlation of actual achieved median oxygen saturations each week from birth until week 4 of age, and follow-up BPs. In view of data presented by DiFiore et al(17) that time spent in hypoxemia (saturations < 80%) during the first 3 days of life is associated with an increased risk of death, we performed an exploratory analyses of whether cumulative time spent in hypoxemia had an impact in BP.

Weekly data for the first 4 weeks of age and an overall model were analyzed on median oxygen saturation and time spent under 80% for systolic and diastolic blood pressures for a total of 10 models. Calculations assumed that the saturation was constant over the 10-second sampled period (i.e., if an infant had a sampled saturation of 79% at one point, she was recorded as having spent 10 seconds with 79% saturation, which may over- or under-estimate time spent in hypoxemia). When there was not a one-to-one correspondence

between the oximeter display values and “actual” SpO2 values, cubic Hermite and quadratic interpolation techniques were used to smooth the SUPPORT oximeter data and calculate the median oxygen saturation achieved.

Statistical Analysis

Descriptive statistics were used for various neonatal and maternal characteristics and were compared for infants in the higher and lower oxygen saturation targets. Frequencies and percentages were calculated for categorical variables with differences in baseline characteristics between oxygen saturation target groups tested for by chi-square and Fisher’s exact test. Medians, means and standard deviations were calculated for continuous variables with differences between groups tested using Mann-Whitney Wilcoxon tests. Mean systolic and diastolic BPs were compared between the lower and higher assigned O_2 saturation target group using general linear mixed modeling, controlling for center and gestational age as fixed effects, and familial clustering as a random effect. With our sample size of 387 individuals, there was 80% power to detect a mean difference as low as 1.27mmHg and 1.16mmHg in systolic and diastolic BP, respectively between randomized target oxygen saturation groups.

This same approach was used to analyze the association between BP and achieved median O_2 saturations, and between BP and time spent under 80% O_2 saturation. BP outcomes were analyzed for the oxygen saturation measurements obtained for the duration of study monitoring during the main trial, and by each week of age from birth to 36 weeks corrected GA. All models were adjusted for GA, sex, race/ethnic group, maternal level of education, SGA status (defined as <10% on the Alexander curves)[18] , ROP defined as stage 3 in zone 1 with or without plus disease and any ROP with plus disease, or stage 2 or greater in zone 2 with plus disease, physiologic bronchopulmonary dysplasia (BPD) defined as need for more than 30% of oxygen or need of positive pressure ventilation at 36 weeks, or any oxygen requirement after 36 weeks if a room air trial was attempted, indomethacin treatment within 24 hours, and body mass index (BMI) at 6-7 years. Further, the model for time spent under hypoxemia was reassessed excluding the 3 plausible outliers (i.e. individuals who spent > 10 hours with saturations <80%) to establish their impact on the outcomes. Analyses were conducted using SAS version 9.4.

Results

Three hundred and eighty-seven children with oxygen saturation data and BP measurements at School-Age were included for analysis (Figure 1). The two O_2 saturation comparison groups had similar baseline characteristics including birth weight, GA, percent small for gestational age (SGA), sex, ethnicity, use of antenatal steroids, maternal diabetes, maternal hypertension, maternal level of education, indomethacin treatment, and BMI (Table 1). Infants in the higher-target group had significantly higher rates of ROP and BPD. The proportion of children who survived to follow-up was similar between groups (96% vs 94%, p=0.50). Fourteen patients did not have BP data at follow-up, therefore were excluded from the analyses.

Examining the outcome first by target oxygen saturation group, we found no difference in systolic or diastolic BP between the two groups. Furthermore, there was no difference between groups in the percentage of children with high blood pressure and hypertension (Table 2). We then evaluated actual achieved median oxygen saturations. There was no difference in BP for each 1% change in actual median achieved weekly O_2 saturation (Table 3).

Finally, an exploratory analysis was conducted to assess whether the duration of time spent < 80% saturation each week in the neonatal period correlated with BP at age 6 (Table 4). We found an association only for the first postnatal week, with an increase in systolic blood pressure of 0.6 mmHg (95% CI 0.02,1.18) for every hour spent under 80% O_2 saturation during the first week of life (Figure 2).

Discussion

To our knowledge, this is the first study exploring the association between neonatal oxygen saturation in extremely preterm infants and blood pressure at early school age. We found a positive correlation between oxygen saturation < 80% in the first postnatal week and increased systolic BP at 6-7 years. Importantly, however, we found no association between lower vs. a higher oxygen saturation target, nor between actual achieved weekly saturations and blood pressure at age 6. Thus, while number of hours with measured oxygen saturations <80% in the first week may be related to higher systolic blood pressure at school age, variation in saturations within the overall target range was not.

We had hypothesized that lower oxygen saturations would be associated with higher BP at follow-up, as experiments have shown that animals exposed to either chronic or intermittent hypoxemia during the neonatal period have decreased arterial compliance, impaired baroreflex control and increased sympathetic activation compared to control animals in room air. Those changes persisted into adult life, causing elevation of systolic BP.[9,19] Similarly, healthy Danish volunteers exposed to chronic hypoxemia developed increased muscle sympathetic nerve activity, with an increase in mean arterial pressure.(10)

In our study, increased duration of hypoxemia in the first postnatal week was associated with increased BP at age 6. This correlation was not present in any other week, and a cumulative effect of prolonged duration of hypoxemia was not seen, therefore as an isolated finding in an exploratory analysis, this should be interpreted with caution. However, animal models have demonstrated an increased susceptibility of the most immature cardiovascular system to hypoxemia. For instance, Del Duca et al(20) demonstrated significant upregulation of genes associated with vascular remodeling in response to neonatal hypoxia in rats. In addition, Ross et al(9) showed decreased arterial compliance and increased systolic arterial pressure in adult rats that were exposed to prolonged hypoxemia in early life. In humans, other early hypoxemic events have also been associated with adverse outcomes; for example, exposure to lower inspired oxygen fractions (FiO_2) in the delivery room and lower oxygen saturations in the first three postnatal days have been associated with increased mortality and severe neurological injury in extremely preterm infants.(17,21,22)

An important finding in our study was that neither assignment to the lower oxygenation target group nor achieved median oxygen saturations were associated with BP at follow-up. The absence of effect from randomization group on BP outcomes could have been influenced by the significant overlap between groups in median oxygen saturation that occurred in the original trial.(13) However, we also found no association between actual median oxygen saturation levels and BP at age 6. Those findings are consistent with other studies that have shown that other neonatal markers of disease such as BPD or ROP are not associated with elevated BP in school-age children and young adults born preterm. (2,6)

There are several limitations to our study. First, this was a retrospective review of a non-randomly selected sub-cohort of survivors that included only a third of the survivors from the main trial, which was not powered for the outcome of BP at 6-7 years. In addition, the NEURO study cohort represents a subgroup of the SUPPORT cohort, in that it was approved and began recruitment after SUPPORT began enrollment, and not all centers participated nor did they launch simultaneously. Second, the number of hours spent under 80% oxygen saturation was extrapolated by oximeter data sampled every 10 seconds, therefore the cumulative time is an estimate. Third, multiple patterns of oxygenation and time periods were compared, with only one association found, therefore, any positive associations must be interpreted with caution. Fourth, although we looked at total time < 80% oxygen saturation per week, it was not feasible to assess the effects of increasing numbers of intermittent hypoxic episodes,(23) which have been associated with higher BP in animal models and children with obstructive sleep apnea.(8,12) Fifth, there is no clinical information available on renal and cardiac diseases, such as kidney size or measurements of renal function, that may affect BP outcomes.

Our study also had many strengths. The sample size was large and allowed us to detect very small differences in BP outcomes by target group, if they were present. It also includes children randomized to two oxygen target groups from birth, with data recorded for most of their in-hospital stay. There is an evidence gap regarding long term cardiovascular effects of hypoxemia in the neonatal period, and our study includes detailed oxygen saturation data in the neonatal period and blood pressure outcomes at age 6 of 387 former extremely preterm individuals, which adds important information on those outcomes.

In conclusion, in this study we found that neither target nor actual median oxygen saturations within the range assigned in this study were associated with BP at school age. However, a longer duration of oxygen saturations below 80% in the first postnatal week may be associated with higher systolic BP. Given the limitations of this analysis noted above, additional studies are required to provide definitive information regarding that finding.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator), Marie Gantz, and Barbara Do (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Abbreviations:

BP	blood pressure
VLBW	very low birth weight
GA	gestational age
ROP	retinopathy of prematurity

BPD bronchopulmonary dysplasia

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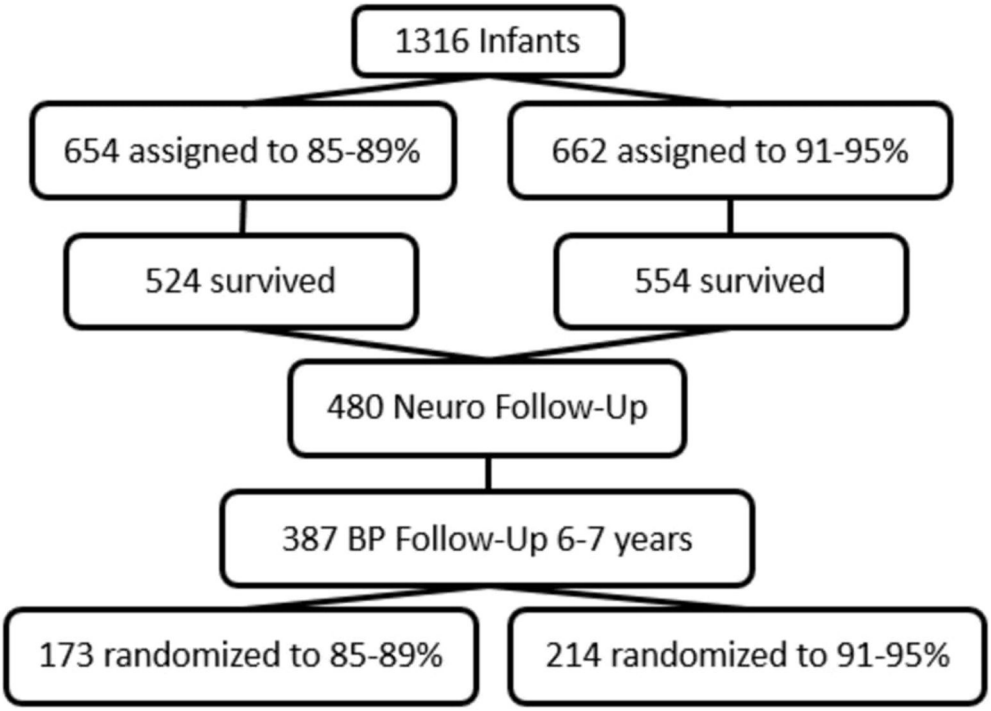

Figure 1.
Flowchart diagram of the original SUPPORT cohort, secondary study and current analysis

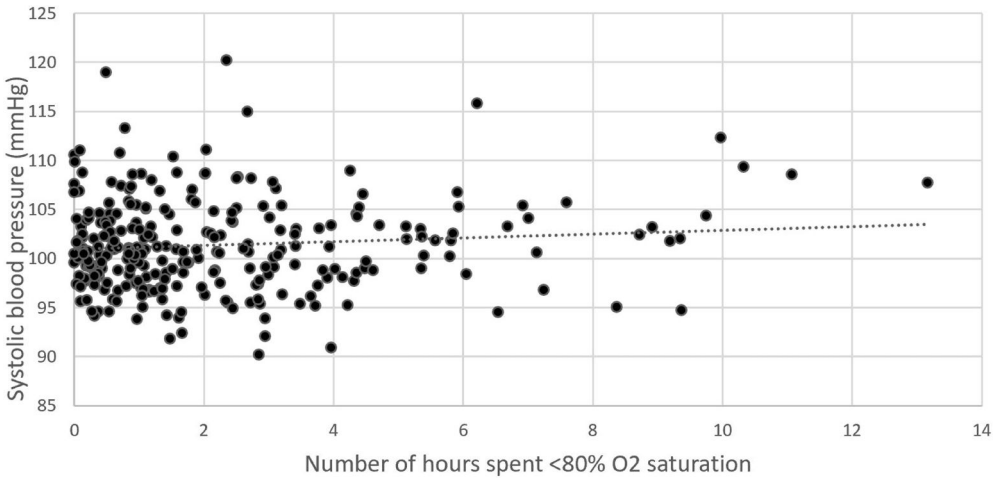

Figure 2.

Linear Association of Hours < 80% Saturation During the First Postnatal Week and Systolic Blood Pressure at Age 6 ; Model adjusted for GA, sex, race/ethnic group, maternal level of education, SGA status (defined as <10% on the Alexander curves), ROP, bronchopulmonary dysplasia (BPD), indomethacin treatment within 24 hours, and body mass index (BMI) at 6-7 years

Table 1.

Baseline Characteristics

Characteristics	Lower O_2 Saturation Target (N=173)	Higher O_2 Saturation Target (N=214)	P
Birthweight (grams)	876 ± 195	854 ± 188	0.27
GA (weeks)	26.4 ± 1	26.2 ± 1	0.12
SGA status (%)	11 (6)	16 (7)	0.69
Male sex (%)	90 (52)	121 (57)	0.41
Ethnicity (%)			0.09
Non-Hispanic White	72 (42)	90 (42)	
Non-Hispanic Black	64 (37)	58 (27)	
Hispanic	34 (20)	58 (27)	
Other / Unknown	3 (2)	8 (4)	
Antenatal Steroids (%)	166 (95)	202 (94)	0.64
Maternal hypertensive disorders (%)	47 (27)	52 (24)	0.56
Maternal level of education (High School graduate) (%)	131 (76)	152 (73)	0.55
Retinopathy of prematurity requiring surgery (%)	8 (5)	29 (14)	<0.01
Physiological Bronchopulmonary Dysplasia (%)	45 (26)	86 (40)	<0.01
Indomethacin treatment within 24 hours of life (%)	52 (30)	60 (28)	0.74
Body Mass Index at 6-7 years	16.3 ± 3.2	15.9 ± 2.7	0.18

Table 2.

Oxygen Saturation Target Assignment and Blood Pressure at Age 6

Characteristics	Lower O_2 Saturation Target (N=173)	Higher O_2 Saturation Target (N=214)	P
Systolic BP (mmHg)	101.3 ± 8.4	100.7 ± 9.2	0.45
High systolic BP (%)	35 (20)	43 (20)	0.99
Systolic hypertension (%)	15 (9)	27 (13)	0.25
Diastolic BP (mmHg)	62.2 ± 8.1	62.8 ± 8.1	0.64
High diastolic BP (%)	33 (19)	48 (23)	0.45
Diastolic hypertension (%)	15 (9)	28 (13)	0.19

Table 3.

Median Oxygen Saturation by Postnatal Week and Blood Pressure at age 6

Postnatal Week	Median Oxygen Saturation (IQR)	Systolic Blood Pressure		Diastolic Blood Pressure	
		Mean Change in BP* (95% CI)	P	Mean Change in BP* (95% CI)	P
Overall study period	93.5 (92-94)	0.17 (−0.48 to 0.82)	0.59	−0.08 (−0.70 to 0.53)	0.78
1 Week of Age	93 (92-95)	−0.40 (−1.13 to 0.32)	0.24	−0.09 (−0.78 to 0.59)	0.76
2 Weeks of Age	93 (92-94)	0.42 (−0.26 to 1.11)	0.19	0.41 (−0.23 to 1.06)	0.18
3 Weeks of Age	93 (92-94)	0.20 (−0.46 to 0.87)	0.50	0.10 (−0.53 to 0.73)	0.73
4 Weeks of Age	93 (92-94)	0.10 (−0.62 to 0.81)	0.75	−0.30 (−0.98 to 0.38)	0.32

*Mean change = decrease or increase in BP (mmHg) for every 1% increase in median oxygen saturation. Model adjusted for GA, sex, race/ethnic group, maternal level of education, SGA status (defined as <10% on the Alexander curves), ROP requiring surgery, bronchopulmonary dysplasia (BPD), indomethacin treatment within 24 hours, and body mass index (BMI) at 6-7 years

Table 4.

Number of Hours Spent Under 80% Oxygen Saturation Levels and Blood Pressure at age 6

Week of Age	Median Number of Hours < 80% (IQR)	Systolic Blood Pressure		Diastolic Blood Pressure	
		Mean Change in BP*† (95% CI)	P	Mean Change in BP*† (95% CI)	P
Overall study period	26.4 (7.1-66.7)	−0001(−0.03 to 0.03)	0.99	−0.0007 (−0.03 to 0.03)	0.96
1 Week of Age	1.6 (0.5-3.4)	0.60 (0.02 to 1.18)	0.04	0.26 (−0.29 to 0.81)	0.29
2 Weeks of Age	3.5 (1.2-7.1)	0.03 (−0.32 to 0.39)	0.82	−0.06 (−0.39 to 0.28)	0.70
3 Weeks of Age	5.8 (2.3-11.4)	−0.04 (−0.28 to 0.19)	0.65	−0.01 (−0.23 to 0.21)	0.91
4 Weeks of Age	6.7 (2.7-13.3)	0.03 (−0.22 to 0.28)	0.71	−0.02 (−0.25 to 0.21)	0.77

*Mean change = decrease or increase in BP (mmHg) for every additional hour spent <80% saturation. Model adjusted for GA, sex, race/ethnic group, maternal level of education, SGA status (defined as <10% on the Alexander curves), ROP requiring surgery, bronchopulmonary dysplasia (BPD), indomethacin treatment within 24 hours, and body mass index (BMI) at 6-7 years.

†Statistical conclusions were not adjusted for multiple comparisons.