Original Investigation

Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants

Christian F. Poets, MD; Robin S. Roberts, MSc; Barbara Schmidt, MD, MSc; Robin K. Whyte, MB; Elizabeth V. Asztalos, MD, MSc; David Bader, MD; Aida Bairam, MD, PhD; Diane Moddemann, MD; Abraham Peliowski, MD; Yacov Rabi, MD; Alfonso Solimano, MD; Harvey Nelson, MSc; for the Canadian Oxygen Trial Investigators

IMPORTANCE Extremely preterm infants may experience intermittent hypoxemia or bradycardia for many weeks after birth. The prognosis of these events is uncertain.

OBJECTIVE To determine the association between intermittent hypoxemia or bradycardia and late death or disability.

DESIGN, SETTING, AND PARTICIPANTS Post hoc analysis of data from the inception cohort assembled for the Canadian Oxygen Trial in 25 hospitals in Canada, the United States, Argentina, Finland, Germany, and Israel, including 1019 infants with gestational ages of 23 weeks 0 days through 27 weeks 6 days who were born between December 2006 and August 2010 and survived to a postmenstrual age of 36 weeks. Follow-up assessments occurred between October 2008 and August 2012.

EXPOSURES Episodes of hypoxemia (pulse oximeter oxygen saturation <80%) or bradycardia (pulse rate <80/min) for 10 seconds or longer. Values were sampled every 10 seconds within 24 hours after birth until at least 36 weeks' postmenstrual age.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of death after 36 weeks' postmenstrual age, motor impairment, cognitive or language delay, severe hearing loss, or bilateral blindness at 18 months' corrected age. Secondary outcomes were motor impairment, cognitive or language delay, and severe retinopathy of prematurity.

RESULTS Downloaded saturation and pulse rate data were available for a median of 68.3 days (interquartile range, 56.8-86.0 days). Mean percentages of recorded time with hypoxemia for the least and most affected 10% of infants were 0.4% and 13.5%, respectively. Corresponding values for bradycardia were 0.1% and 0.3%. The primary outcome was ascertained for 972 infants and present in 414 (42.6%). Hypoxemic episodes were associated with an estimated increased risk of late death or disability at 18 months of 56.5% in the highest decile of hypoxemic exposure vs 36.9% in the lowest decile (modeled relative risk, 1.53; 95% CI, 1.21-1.94). This association was significant only for prolonged hypoxemic episodes lasting at least 1 minute (relative risk, 1.66; 95% CI, 1.35-2.05 vs for shorter episodes, relative risk, 1.01; 95% CI, 0.77-1.32). Relative risks for all secondary outcomes were similarly increased after prolonged hypoxemia. Bradycardia did not alter the prognostic value of hypoxemia.

CONCLUSIONS AND RELEVANCE Among extremely preterm infants who survived to 36 weeks' postmenstrual age, prolonged hypoxemic episodes during the first 2 to 3 months after birth were associated with adverse 18-month outcomes. If confirmed in future studies, further research on the prevention of such episodes is needed.

Editorial page 568

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Canadian Oxygen Trial investigators are listed at the end of this article.

Corresponding Author: Christian F. Poets, MD, Department of Neonatology, Tuebingen University Hospital, Calwerstrasse 7, 72076 Tübingen, Germany (christian-f.poets@med.uni-tuebingen.de).

JAMA. 2015;314(6):595-603. doi:10.1001/jama.2015.8841

Almost all extremely preterm infants (those born at <28 weeks' gestation) experience intermittent hypoxemia and bradycardia during their stay in the neonatal intensive care unit.[1] Although many such episodes are related to apnea of prematurity, a significant number of episodes occur in mechanically ventilated infants because of cardiorespiratory instability.[2] The relationship between neonatal hypoxemia or bradycardia and later neurodevelopment in this population of high-risk preterm infants is uncertain.[3]

In the multicenter Canadian Oxygen Trial (COT),[4] extremely preterm infants were randomly assigned to lower (85%-89%) or higher (91%-95%) pulse oximeter oxygen saturation (Spo_2) targets. As in routine neonatal intensive care, Spo_2 and pulse rate were continuously monitored. However, in COT, the recorded oxygen saturation and pulse rate values were downloaded and submitted to the coordinating center for analysis. This provided the opportunity to separately examine the relationships between episodes of hypoxemia (Spo_2 <80%) or bradycardia (pulse rate <80/min) and protocol-specified outcomes of COT participants. The main study question in this post hoc analysis was as follows: among extremely preterm infants who survive to a postmenstrual age of 36 weeks, what are the associations between neonatal hypoxemia or bradycardia and the risks of late death after 36 weeks' postmenstrual age or disability at 18 months' corrected age?

Methods

COT enrolled 1201 infants of 23 to 27 weeks' gestation within 24 hours of birth after excluding those not considered viable; those who had congenital malformations, cyanotic heart disease, or pulmonary hypertension; and those unlikely to be available for long-term follow-up.[4] Race or ethnic group was self-reported using predetermined options.[4] This baseline characteristic was provided to describe the study population. Infants were randomized to target ranges of 85% to 89% or 91% to 95% on study pulse oximeters that displayed offset saturation values between 84% and 96%.[4] Follow-up was targeted for a corrected age of 18 months, with a window of 18 to 21 months. Efforts to conduct assessments continued beyond this window if necessary.[4] The research ethics boards of all clinical centers approved the protocol, and written informed consent was obtained from a parent or guardian of every study infant.

Since infants who die early cannot develop the longer-term outcomes of interest, this analysis cohort was limited to COT participants who survived to 36 weeks' postmenstrual age.

Study Oximetry and Analysis of Saturation and Pulse Rate Data

The implementation of study oximetry has been described.[4] The averaging time on all study oximeters was set to 16 seconds and the displayed data sampled and stored every 10 seconds. eFigure 1 in the Supplement provides a schematic of how oximeter data were averaged and sampled. Study oximetry was continued until 36 weeks' postmenstrual age irrespective of the need for supplemental oxygen, and until 40 weeks in those still receiving supplemental oxygen or any other respiratory support at 35 weeks' postmenstrual age. Study oximetry was stopped earlier if infants were discharged home.

Designated research staff in the clinical centers downloaded and submitted the stored saturation and pulse rate data to the coordinating center every 3 to 4 weeks until study oximetry was discontinued. Streams of downloaded data (Spo_2 and pulse rate) were screened for validity; invalid measurements were discarded (including those showing values of 0 or any of the oximeters' exception flags for displaced sensor, ambient light, interference, or low perfusion). Episodes of hypoxemia (defined as a single value or consecutive values of Spo_2 <80%) and equivalent episodes of bradycardia (pulse rate <80/min) were identified. For each episode, the number of consecutive 10-second data values below the threshold was defined as the episode length, with episode duration (in minutes) estimated as (length × 10) ÷ 60. The area under the curve (AUC) for an episode was calculated as the product of the episode duration in minutes times the average depth below the threshold for the episode. An infant's exposure to hypoxemia was expressed first as the percentage of time with hypoxemia (100 × total duration of hypoxemic episodes/total duration of recording) and second as the average AUC per day. Equivalent calculations were conducted separately for bradycardic episodes. Percentage of time with hypoxemia or bradycardia was calculated for short and long episodes (1-5 and ≥6, respectively, consecutive values below threshold). Six consecutive values below threshold in 10-second samples approximate a duration of 1 minute. These values were also calculated by postnatal age in 2-weekly intervals.

Outcomes

All outcomes in this study had been prespecified in the original COT study.[4] However, the present analysis was of survivors to 36 weeks' postmenstrual age. Thus, the primary composite outcome was late death or disability, defined as death between 36 weeks' postmenstrual age and 18 months' corrected age or survival with 1 or more of the following: motor impairment, cognitive or language delay, severe hearing loss (prescription of hearing aids or cochlear implants), and bilateral blindness (corrected visual acuity <20/200 in the better eye).[4] Secondary outcomes were motor impairment, cognitive or language delay, and severe retinopathy of prematurity.

Motor impairment was defined as level 2 or higher in the Gross Motor Function Classification System[5]; ie, inability to pull to stand, cruise, or walk. Cognitive or language delay was defined as a composite cognitive or language score of less than 85 (1 SD below the mean of 100) on the *Bayley Scales of Infant and Toddler Development*, Third Edition.[6] The cognitive score was assumed to be less than 85 if the child could not be tested because of severe developmental delay or autism. Severe retinopathy of prematurity

was defined as unilateral or bilateral disease of stage 4 or 5.[7] Infants were also classified as having severe retinopathy if they received cryotherapy or laser therapy in at least 1 eye or intravitreal injection with an antivascular endothelial growth factor agent. For infants who were discharged before the complete progression and subsequent regression of retinopathy, the worst disease stage and any retinal therapy received were documented during the follow-up visit.

Cases of severe retinopathy were diagnosed at a median postmenstrual age of 37.6 weeks, and diagnosis could predate some of the oximetry data. Therefore, for this outcome only, aggregate measures of hypoxemia and bradycardia were truncated at the time when severe retinopathy was diagnosed in infants who developed it and at a postmenstrual age of 37.6 weeks in infants who did not develop severe retinopathy.

Statistical Analysis

The strength of the relationship between percentage of time with hypoxemia and the primary outcome as well as each of the 3 secondary outcomes was assessed by logistic regression. Models were fitted with the dichotomous outcome as the dependent variable and percentage of time with hypoxemia as the continuous independent variable. The regression coefficient associated with the hypoxemia variable provided an estimate of the risk gradient (log odds scale), and its standard error yielded a formal significance test and confidence interval. Additional independent variables were included in the model to adjust for a prespecified set of baseline covariates (gestational age, sex, primary caregiver's educational attainment, use of antenatal corticosteroids, multiple birth, and study center). To visualize the fit of these models, the data were subdivided into deciles of percentage of time with hypoxemia and the observed outcome rate plotted against the mean percentage of time with hypoxemia for each decile. The fitted unadjusted and adjusted models were superimposed on the graphical data to show the fit. Equivalent analyses were performed for bradycardia. Next, the relative prognostic importance of percentage of time with hypoxemia was compared with percentage of time with bradycardia. Both exposure variables were entered in a stepwise logistic model such that the stronger of the 2 would be selected at the first step and, depending on the residual predictive information of the remaining unselected variable, it would enter at the second step. These analyses showed that bradycardia offered no significant prognostic information in addition to hypoxemia. Therefore, bradycardia was not included in subsequent analyses.

The risk gradients with the AUC measure of hypoxemic exposure were examined using a logistic model adjusted for the same baseline covariates. The relative prognostic strength of percentage of time with hypoxemia and hypoxemia AUC per day was investigated by offering both variables in a stepwise fashion to a model already containing the baseline covariates.

To determine whether the risk gradients changed with the duration of the hypoxemic episodes, the percentage of time with hypoxemia was computed separately for episodes of varying lengths (1-2, 3-5, 6-10, 11-15, 16-20, or >20 and ≤5 vs ≥6 consecutive 10-second Spo_2 values <80%). Stepwise logistic models were used to determine the relative prognostic importance of these episode length variables. A similar analysis (stratified by gestational age at birth) was conducted to assess the influence of postnatal age by calculating percentage of time with hypoxemia by 2-week age intervals to a maximum of 10 weeks.

Infants in this analysis cohort had been randomly assigned to 2 oxygen saturation target ranges (85%-89% vs 91%-95%). Therefore, a test for a potential interaction between the COT treatment allocation and exposure to hypoxemia on the outcome of late death or disability was performed. A binary indicator variable for the COT treatment allocation and a product term of COT treatment times percentage of time with Spo_2 of less than 80% were added to the adjusted logistic model. The coefficient associated with the product term (interaction) in the logistic model provided a formal test indicating whether the risk gradient differed by COT oxygen saturation target range.

Risk gradients were calculated from the logistic model as odds ratios contrasting the highest decile of hypoxemic exposure with the lowest decile based on the mean percentage of time with hypoxemia in each of the 2 respective deciles. Poisson regression with robust variance estimation was used to provide the corresponding risk gradients as relative risks.

All statistical analyses were done using SAS version 9.3 (SAS Institute Inc). All *P* values were 2-sided and considered significant if $P < .05$.

Results

Of the 1201 COT participants, 1035 survived to a postmenstrual age of 36 weeks and were eligible for this study. Six infants had missing outcome data and 10 had no valid Spo_2 data available, leaving 1019 (98.5%) in the analysis cohort. **Table 1** summarizes the clinical characteristics and rates of adverse outcomes of the study population.[8] The primary outcome of late death after 36 weeks' postmenstrual age or disability at 18 months was ascertained in 972 infants and present in 414 (42.6%).

Valid oximetry recordings were available for a median duration of 68.3 days (interquartile range [IQR], 56.8-86.0 days). The amount of recorded data discarded because of an exception code generated by the study oximeter was 0.2%. Median episode length was 3.3 (IQR, 2.5-4.4) consecutive 10-second Spo_2 values of less than 80% for hypoxemia, and 1.9 (IQR, 1.7-2.2) consecutive 10-second pulse rate values of less than 80/min for bradycardia (**Table 2**). Hypoxemia was more prevalent than bradycardia (median, 3.34% [IQR, 1.55%-6.13%] of total recording time vs 0.12% [IQR, 0.085%-0.17%]). Hypoxemic episodes lasting for 6 or more consecutive 10-second values (ie, lasting for approximately 1 minute or longer) occurred at a median rate of 12.1 (IQR, 4.8-23.8) episodes per day compared with 73.5 (IQR, 37.3-113.3) epi-

Table 1. Clinical Characteristics and Outcomes of Study Participants[a]

Characteristics	No. (%) of Study Cohort (n = 1019)
Mothers at infants' birth	
Age, mean (SD), y	30.8 (6.3)
Race or ethnic group	
White	677 (66.4)
Black	174 (17.1)
Asian	105 (10.3)
Other or unknown	63 (6.2)
Antenatal corticosteroids	922 (90.5)
Cesarean delivery	627 (61.5)
Infants at birth	
Birth weight, mean (SD), g	855 (189)
Gestational age, mean (SD), wk	25.8 (1.1)
Female	479 (47.0)
Birth weight <10th percentile for gestational age[b]	79 (7.8)
Born at study hospital	941 (92.3)
Singleton birth	699 (68.6)
Apgar score at 5 min, median (IQR)	8 (6-8)
Chest compressions in the delivery room	68 (6.7)
First temperature after admission, mean (SD), °C	36.5 (0.8)
Status at enrollment	
Age at enrollment, median (IQR), h	17.8 (11.8-22.1)
Supplemental oxygen	366 (35.9)
Any use of positive airway pressure	986 (96.8)
Endotracheal tube in situ	770 (75.6)
Receipt of surfactant	879 (86.3)
Status at follow-up	
Corrected age of surviving infants at follow up, median (IQR), mo	18.6 (18.2-19.6)
Primary caregiver level of education	
Did not finish high school	116 (11.4)
High school graduate	371 (36.4)
College/university graduate	509 (49.9)
Unknown	23 (2.3)
Outcomes at follow-up	
Late death or disability[c]	414 (42.6)
Cognitive or language delay[d]	380 (40.2)
Motor impairment[e]	61 (6.3)
Severe retinopathy of prematurity[f]	130 (13.1)

Abbreviation: IQR, interquartile range.

[a] Data are expressed as No. (%) of participants unless otherwise indicated. These data are for the 1019 infants who survived to 36 weeks' postmenstrual age and had adequate data for the determination of 1 or more of the study outcomes—late death or disability, cognitive or language delay, motor impairment, and severe retinopathy of prematurity—at a corrected age of 18 to 21 months.

[b] The 10th percentile for gestational age in a healthy population was reported by Kramer et al.[8]

[c] A total of 972 children had data for this outcome.

[d] A total of 945 children had data for this outcome.

[e] A total of 966 children had data for this outcome.

[f] A total of 993 children had data for this outcome.

sodes per day for shorter episodes. The majority of the shorter episodes lasted for only 1 or 2 consecutive 10-second values. Bradycardia lasting for approximately 1 minute or longer was rare, occurring on average once every 5 days (Table 2).

Figure 1 shows the relationship between each study outcome and percentage of time with hypoxemia and bradycardia. The mean percentage of time with hypoxemia among infants contributing data to the primary outcome of late death or disability ranged from 0.4% in the lowest decile to 13.5% in the highest. Corresponding results for bradycardia were 0.1% and 0.3%. eTable 1 in the Supplement summarizes the observed frequencies of hypoxemia and bradycardia in each of the deciles of exposure. The probability of each adverse outcome increased significantly with the percentage of time with hypoxemia. Estimated rates of late death or disability at 18 months from the adjusted model at the mean values of percentage of time with hypoxemia were 36.9% and 56.5%, respectively, for the lowest and highest deciles of exposure. Risk gradients were much smaller for percentage of time with bradycardia, with motor impairment showing the only statistically significant relationship. For all outcomes, stepwise modeling consistently selected exposure to hypoxemia over bradycardia on the first step, with bradycardia offering no additional significant prognostic information. Therefore, bradycardia was not included in subsequent analyses.

Table 3 summarizes the risk gradients of outcomes with percentage of time with hypoxemia and the effects of the duration of each episode. For infants in the highest decile of exposure to intermittent hypoxemia, the odds ratios and relative risks were increased for all adverse outcomes compared with infants in the lowest decile of exposure to intermittent hypoxemia. For the primary outcome of late death or disability, the modeled relative risk was 1.53 (95% CI, 1.21-1.94) for infants in the highest vs lowest decile of exposure. For each outcome, the odds ratios and relative risks were lower and nonsignificant for short (<1-minute) episodes of hypoxemia, but higher and significant for long (≥1-minute) episodes. For the primary outcome, the relative risk was 1.01 (95% CI, 0.77-1.32) for short hypoxemic episodes vs 1.66 (95% CI, 1.35-2.05) for long hypoxemic episodes.

eTable 2 in the Supplement shows the equivalent analysis for AUC as predictor of outcome with similar results. Based on this observation and supportive modeling including both exposure variables, it was determined that AUC offered no meaningful advantage over percentage of time with hypoxemia and was more difficult to compute. The remainder of the analysis was thus confined to percentage of time with hypoxemia.

The differences in exposure to hypoxemia between infants who did and did not develop adverse outcomes became greater with increasing postnatal age ($P < .05$) (eFigure 2, left panels, and eTable 3 in the Supplement). The greatest risk gradients were seen at 9 to 10 weeks after birth ($P<.001$ for interaction) (eFigure 2, right panels, and eTable 4 in the Supplement), both in more and less mature infants (≥26 vs ≤25 weeks' gestational age). Logistic modeling sup-

ported these observations, with percentage of time with hypoxemia in postnatal weeks 9 to 10 consistently selected first over earlier 2-week intervals.

The association between exposure to long hypoxemic episodes and the primary outcome of death after a postmenstrual age of 36 weeks or disability at 18 months was stronger for infants randomly assigned to an oxygen saturation target range of 91% to 95% than for those assigned to a target range of 85% to 89% (adjusted P = .001 for interaction) (**Figure 2** and eTable 5 in the Supplement).

Discussion

This post hoc study examined associations between intermittent hypoxemia or bradycardia and the primary composite outcome of late death or disability at a corrected age of 18 months for extremely preterm infants who survived to a postmenstrual age of 36 weeks. The risk of this outcome increased with the percentage of time the infants experienced intermittent hypoxemia. The risks of all secondary outcomes, motor impairment, cognitive or language delay, and severe retinopathy of prematurity, were also increased. Intermittent bradycardia did not significantly add to the risk of adverse outcome, suggesting that bradycardia in the absence of concurrent hypoxemia may not be of prognostic importance. The severity of intermittent hypoxemia, expressed as the AUC, added little prognostic value to the simpler measure of the percentage of time spent with hypoxemia. However, the duration of the hypoxemic episodes mattered: only those lasting for approximately 1 minute or more were significantly associated with an increased risk of an adverse outcome. Associations between hypoxemic exposure and adverse outcomes were stronger at later postnatal ages and for infants who had been randomly assigned to a target oxygen saturation range of 91% to 95% compared with those who had been assigned to a target range of 85% to 89%. In the original COT cohort, infants who had been allocated to the lower target range spent significantly more time with oxygen saturations below 80% than infants who had been assigned to the higher target range, but mortality rates from birth to a corrected age of 18 months were similar in the 2 groups.[4] In the present subgroup of COT participants who survived to a postmenstrual age of 36 weeks, prolonged hypoxemia—once it occurred—appeared to be of greater prognostic importance in infants who were maintained at higher as opposed to lower oxygen saturations. Episodes of prolonged hypoxemia with Spo_2 below 80% represented a greater drop of saturations from baseline values in infants who were maintained at higher as opposed to lower saturations and may suggest a more severe disturbance of oxygen homeostasis. We speculate that this phenomenon may explain the greater prognostic value of prolonged intermittent hypoxemia in survivors to 36 weeks' postmenstrual age who were randomly assigned to the higher compared with the lower oxygen saturation target range.

Only Di Fiore et al[9] have so far used similar methods to determine the relationship between hypoxemic episodes and the development of severe retinopathy of prematurity. Their findings are consistent with those shown here for this neonatal morbidity. Other previous investigators have studied fewer than 100 patients,[10-12] analyzed pulse oximetry data only once before discharge home,[13] or correlated nursing records of apnea with neurologic outcome.[14]

Intermittent hypoxemia of extremely immature infants is attributable not only to apnea of prematurity but also to the cardiopulmonary instability commonly seen in mechanically ventilated infants.[2,15] Therefore, the present data provide more comprehensive information on the relationship between intermittent hypoxemia and adverse outcomes than studies that focus solely on apnea.

Although study oximeters in COT were modified to display saturation values between 88% and 92% that were either 3% above or below the true values,[4] saturation values below 80% were not affected by this masking feature. A cutoff of 80% was chosen because this threshold is consistent with previous studies that defined hypoxemia in preterm infants.[9,11,16] Associations between exposure to hypoxemia and adverse outcomes may differ depending on the definition of hypoxemia. However, episodes of hypoxemia with Spo_2 below 80% that last for at least 1 minute are severe and never desired goals of neonatal intensive care.

Table 2. Characteristics of Episodes of Hypoxemia and Bradycardia[a]

Characteristics	Median (IQR)	
	Episodes of Hypoxemia (Spo_2 <80%)	Episodes of Bradycardia (Pulse Rate <80/min)
Episode length[b]	3.3 (2.5-4.4)	1.9 (1.7-2.2)
Rate of episodes/d, by episode length[b]		
Any length	88.4 (46.5-138.2)	5.3 (3.9-7.4)
≤5	73.5 (37.3-113.3)	5.0 (3.7-6.9)
≥6	12.1 (4.8-23.8)	0.23 (0.14-0.39)
1-2	56.1 (28.9-90.6)	4.4 (3.2-5.9)
3-5	14.2 (7.5-24.4)	0.64 (0.45-1.0)
6-10	6.5 (2.9-12.6)	0.17 (0.10-0.27)
11-15	2.5 (0.88-4.8)	0.037 (0.015-0.069)
16-20	1.1 (0.25-2.5)	0.011 (0-0.028)
≥21	1.4 (0.34-3.7)	0.0089 (0-0.024)
Time spent in episodes of any length, %	3.34 (1.55-6.13)	0.12 (0.085-0.17)
Area under the curve per d[c]	357 (159-752)	29 (22-40)

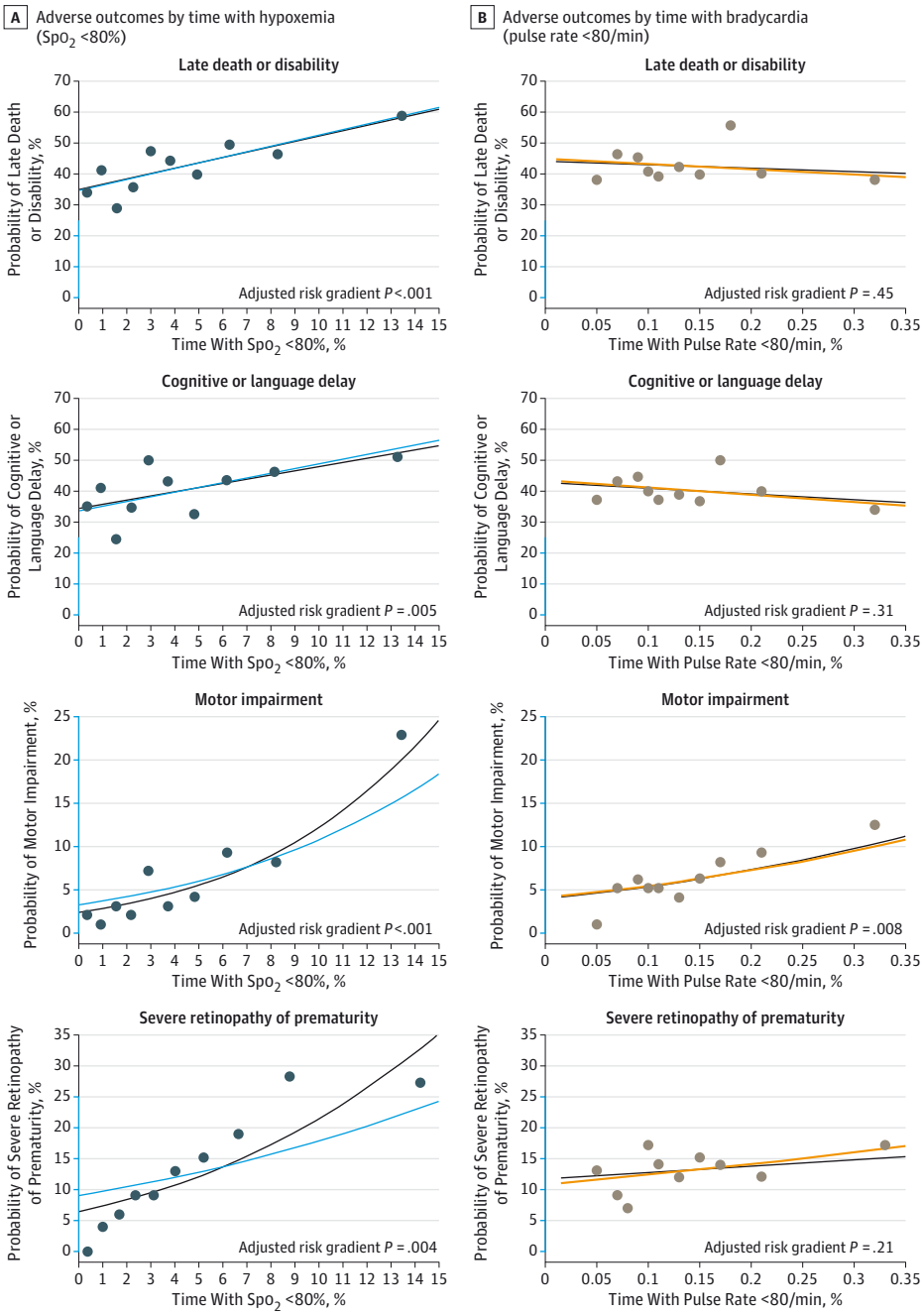
Abbreviations: IQR, interquartile range; Spo_2, pulse oximeter oxygen saturation.

[a] Downloaded saturation and pulse rate data were available for a median duration of 68.3 (IQR, 56.8-86.0) days.

[b] Episode length was defined as the number of consecutive readings, sampled every 10 seconds, with Spo_2 of less than 80% or pulse rate of less than 80/min.

[c] The area under the curve for each hypoxemic episode was calculated as the episode duration in minutes × the average depth of the Spo_2 curve below 80%, summed over all episodes and expressed as a mean per day. An equivalent calculation was applied to bradycardic episodes. The units associated with area under the curve are percentage saturation – minutes for hypoxemic episodes and beats per minute – minutes for bradycardic episodes.

Figure 1. Adverse Outcome Rates by Deciles of Percentage of Time With Hypoxemia or Bradycardia



The 4 panels on the left show the relationships between the percentage of time with pulse oximeter oxygen saturation (Spo_2) of less than 80% and the primary outcome of late death or disability as well as the 3 secondary outcomes. Regression models were fitted with the respective dichotomous outcome as the dependent variable and percentage of time with hypoxemia as the continuous independent variable. To visualize the fit of these models, the data were subdivided into deciles of percentage of time with hypoxemia and the observed outcome rate plotted against the mean percentage of time with hypoxemia for each decile. The 4 panels on the right show the equivalent relationships between the 4 outcomes and the independent variable percentage of time with pulse rate of less than 80/min. The black curves show the fit of the unadjusted logistic regression models. The blue (A) or orange (B) curves show the fit of the logistic models after adjustment for gestational age, sex, primary caregiver level of educational attainment, use of antenatal corticosteroids, multiple birth, and study center. Zero to 25% probability of outcome is shown in blue on each y-axis. Risk gradient refers to the model parameter associated with the exposure variable (percentage of time with Spo_2 <80% or pulse rate <80/min). The significance of each risk gradient was computed from the estimated coefficient associated with the respective exposure variable (Wald χ^2) for the adjusted logistic model. The raw data for the decile points are provided in eTable 1 in the Supplement. Sample sizes varied by outcome (eTable 1). For the primary outcome of late death or disability, 972 infants were included in the analyses for both hypoxemia and bradycardia.

The main limitation of this study is its post hoc design. Thus, the results can only generate hypotheses for future research. Future studies should be designed prospectively to explore temporal relationships between the development of neonatal brain or lung injury and intermittent hypoxemia. Prolonged intermittent hypoxemia may contribute to neurodevelopmental impairment. Alternatively, prolonged hypoxemia may be a feature of infants who are destined to develop impairments: persistent, profound, and prolonged desaturations may be a consequence of acquired brain or lung injury.

If prolonged intermittent hypoxemia is confirmed in future studies as a cause and not just a marker of adverse outcome, it may be preventable. Neonatal caffeine therapy improves motor skills and appears to decrease the risk of developmental coordination disorder to age 5 years.[17-19] Because caffeine reduces apnea and assists in the weaning of infants from respiratory support,[20,21] caffeine may exert its beneficial effects on motor disability, at least in part, by preventing hypoxemic episodes. At present, data on the effects of caffeine on hypoxemia are conflicting.[22,23] Insufficiently tested strategies to reduce intermittent hypoxemia in

Table 3. Time With Hypoxemia as a Predictor of Outcome

Outcomes	All Hypoxemic Episodes			Episode Length ≤5[a]			Episode Length ≥6[a]		
	OR (95% CI)[b]	RR (95% CI)[c]	*P* Value	OR (95% CI)[b]	RR (95% CI)[c]	*P* Value	OR (95% CI)[b]	RR (95% CI)[c]	*P* Value
Late death or disability	2.62 (1.50-4.58)	1.53 (1.21-1.94)	<.001	1.04 (0.61-1.77)	1.01 (0.77-1.32)	.88	3.40 (1.95-5.93)	1.66 (1.35-2.05)	<.001
Cognitive or language delay	2.25 (1.28-3.95)	1.47 (1.13-1.90)	.005	0.96 (0.56-1.64)	0.96 (0.72-1.29)	.87	2.88 (1.65-5.02)	1.61 (1.29-2.03)	<.001
Motor impairment	5.31 (2.34-12.04)	3.59 (2.02-6.40)	<.001	2.27 (0.90-5.74)	1.90 (0.90-4.04)	.08	5.20 (2.48-10.92)	3.51 (2.16-5.72)	<.001
Severe retinopathy of prematurity	2.96 (1.42-6.18)	1.95 (1.22-3.11)	.004	1.84 (0.86-3.95)	1.46 (0.86-2.47)	.12	2.95 (1.47-5.90)	1.93 (1.26-2.98)	.002

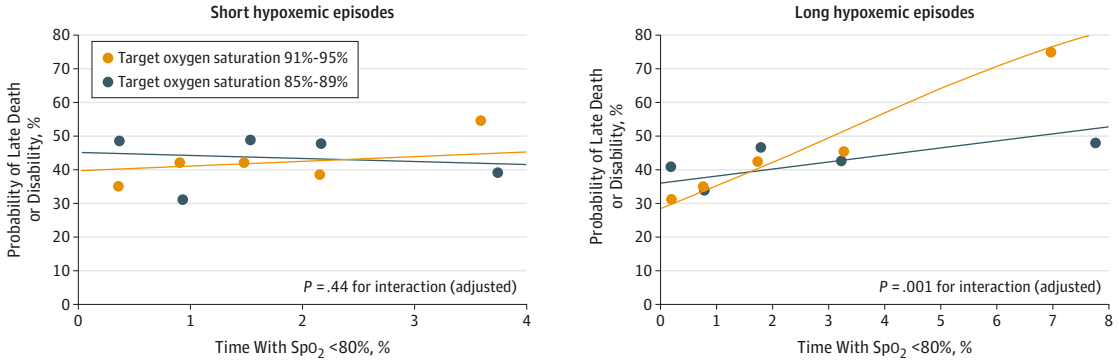
Abbreviations: OR, odds ratio; RR, relative risk; Spo_2, pulse oximeter oxygen saturation.

[a] Episode length was defined as the number of consecutive readings, sampled every 10 seconds, with Spo_2 of less than 80%. The subdivision at 6 consecutive readings equates to an episode length of approximately 1 minute.

[b] Highest decile relative to lowest decile, adjusted for antenatal corticosteroids, gestational age, sex, multiple birth, primary caregiver level of educational attainment, and study center. For the outcome of late death or disability, the means for the highest and lowest deciles of exposure to Spo_2 of less than 80% were for episode length of 5 or lower, 4.4% and 0.2% of time and for episode length of 6 or higher, 9.7% and 0.1% of time. Similar values apply to the other outcomes. See eTable 1 in the Supplement for data on all hypoxemic episodes.

[c] Equivalent relative risks were estimated by Poisson regression.

Figure 2. Association Between Exposure to Short and Long Hypoxemic Episodes and Late Death or Disability by Oxygen Saturation Target Range



Infants in this analysis cohort had been randomly assigned to 1 of 2 oxygen saturation target ranges (85%-89% vs 91%-95%). The left panel shows the relationships between the primary outcome and the percentage of time with pulse oximeter oxygen saturation (Spo_2) of less than 80% lasting for 5 or fewer consecutive 10-second readings, separately for infants assigned to the lower target range (blue) and those assigned to the higher target range (orange). The right panel shows the equivalent relationships for hypoxemic episodes lasting for 6 or more consecutive 10-second readings or approximately 1 minute or longer. The continuous lines represent the predicted probabilities of experiencing the primary outcome. These probabilities were derived from the adjusted logistic model that included a binary indicator variable for the Canadian Oxygen Trial (COT) treatment allocation and a product term of COT treatment × percentage of time with Spo_2 of less than 80%. The coefficient associated with the product term (interaction) in the logistic model provided a formal test indicating whether the risk gradient differed by COT oxygen saturation target range. To visualize the fit of the observed data, the population was subdivided into quintiles based on percentage of time with Spo_2 of less than 80% and then by COT saturation target range. Each subgroup (defined by quintile and COT target range) provided a data point in the graph with the observed outcome rate at 18 months' corrected age plotted against the subgroup mean percentage of time with Spo_2 of less than 80%. The number of infants included for both short and long hypoxemic episodes was 489 for the lower saturation target range and 483 for the higher target range. Raw data are provided in eTable 5 in the Supplement.

extremely preterm infants such as high-dose caffeine,[24] specific ventilator strategies,[25] or doxapram administration[26] may warrant further study.

Finally, should the observation be confirmed in future research that episodes of hypoxemia lasting less than 1 minute are not associated with adverse outcomes in extremely preterm infants, this would be important information for both clinicians and parents.

Conclusions

Among extremely preterm infants who survived to 36 weeks' postmenstrual age, prolonged hypoxemic episodes during the first 2 to 3 months after birth were associated with adverse 18-month outcomes. If these observations are confirmed in future studies, further research on the prevention of such episodes will be needed.

ARTICLE INFORMATION

Author Affiliations: Department of Neonatology, Tuebingen University Hospital, Tuebingen, Germany (Poets); Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada (Roberts, Schmidt, Nelson); Division of Neonatology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia (Schmidt); Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada (Whyte); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

(Asztalos); Department of Neonatology, Bnai Zion Medical Center, Haifa, Israel (Bader); Centre Hospitalier Universitaire de Quebec, Quebec City, Quebec, Canada (Bairam); Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Canada (Moddemann); Royal Alexandra Hospital, Edmonton, Alberta, Canada (Peliowski); Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada (Rabi); Department of Pediatrics, University of British Columbia, Vancouver, Canada (Solimano).

Author Contributions: Mr Roberts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Poets, Roberts, Schmidt, Whyte, Bairam, Nelson.
Acquisition, analysis, or interpretation of data: Roberts, Schmidt, Whyte, Asztalos, Bader, Moddemann, Peliowski, Rabi, Solimano, Nelson.
Drafting of the manuscript: Poets, Roberts, Schmidt, Whyte.
Critical revision of the manuscript for important intellectual content: Asztalos, Bader, Bairam, Moddemann, Peliowski, Rabi, Solimano, Nelson.
Statistical analysis: Roberts.
Obtained funding: Roberts, Schmidt, Whyte, Asztalos, Rabi, Solimano.
Administrative, technical, or material support: Poets, Schmidt, Whyte, Bader.
Study supervision: Poets, Roberts, Schmidt, Whyte.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Poets reports grants from Chiesi Farmaceutici SpA and Masimo. Mr Roberts and Dr Schmidt report receipt of grants from the Canadian Institutes of Health Research. Dr Rabi reports a patent with royalties paid by Masimo (this technology was not used in the current study). Mr Nelson reports receipt of a consultant fee from the Canadian Institutes of Health Research. No other disclosures were reported.

Canadian Oxygen Trial Investigators: (Study sites are listed according to the number of infants they enrolled.) *Mount Sinai Hospital, Toronto, Ontario, Canada*: Prakesh Shah, MSc, MBBS, MD, DCH, MRCP, FRCPC; Leanne Brown, BSc(H), RRT; Lisa Wenger, RRT/AA; Samantha Frye, BSc(H), RRT; Francesca Imbesi, HBSc, RRT; Edmond Kelly, MB, BCh, BAO, DCH, FAAP. *McMaster University Medical Center, Hamilton, Ontario, Canada*: Judy D'Ilario, RN; Madan Roy, MD, MBBS, MRCP, FRCPC; Barbara Schmidt, MD, MSc, FRCPC; Joanne Dix, RN, CNS; Beth Adams, PhD; Janice Cairnie, RN; Patrice Gillie, RN, BScN. *Sunnybrook Health Sciences Center, Toronto, ON, Canada*: Elizabeth V. Asztalos, MD, MSc, FRCPC; Marilyn Hyndman, RRT, MAppSc (Resp); Maralyn Lacy, BSc, RN; Denise Hohn, OT Reg(Ont); Laura Cooper Kruk, MSc (OT), OT Reg (Ont). *Pennsylvania Hospital, Philadelphia*: Soraya Abbasi, MD; Toni Mancini, RN, BSN, CCRC; Emidio Sivieri, MS.E; Kathleen Finnegan, MEd. *Centre Hospitalier Universitaire de Quebec, Quebec City, Canada*: Aida Bairam, MD, PhD; Sylvie Bélanger, MD, FRCPC; Marianne Deschenes, MD; Annie Fraser, MPs. *The Ottawa Hospital and Children's Hospital of Eastern Ontario, Ottawa, Canada*: JoAnn Harrold, MD, FRCPC; Jane Frank, RN; Julie Barden, RN. *IWK Health Centre, Halifax, Nova Scotia, Canada*: Robin Whyte, MBBS, FRCPC; Michael Vincer, MD, FRCPC; Sharon Stone, RN. *Foothills Medical Centre and Alberta Children's Hospital, Calgary, Canada*: Yacov Rabi, MD, FRCPC; Reg Sauve, MD, MPH, FRCPC; Danielle Cyr, BHSc; Heather Christianson, BA; Deborah Anseeuw-Deeks, BN; Dianne Creighton, PhD, RPsych. *Children's & Women's Health Centre of British Columbia, Vancouver, Canada*: Alfonso Solimano, MD, FRCPC; Lindsay Colby, BScN, RN, MSN(c); Arsalan Butt, MSc; Anne Synnes, MDCM, MHSC, FRCPC; Meredith Peterson, RRT. *Hospital of the University of Pennsylvania, Philadelphia*: Barbara Schmidt, MD, MSc, FRCPC; Aasma Chaudhary, BS, RRT; Hallam Hurt, MD; Danielle Foy, CRNP, MSN; Kristina Ziolkowski, CMA; Marsha Gerdes, PhD; Judy Bernbaum, MD. *Royal Alexandra Hospital, Edmonton, Alberta, Canada*: Abraham Peliowski, MD, FRCPC, FAAP; Manoj Kumar, MBBS, MD, MSc; Leonora Hendson, MBBCh, MSc; Melba Athaide, RN, BScN; Jill Tomlinson, CHIM. *University Children's Hospital of Tuebingen, Germany*: Christian F. Poets, MD; Dirk Bassler, MD, MSc; Jutta Armbruster, RN. *FUNDASAMIN, Buenos Aires, Argentina*: Nestor Vain, MD; Cecilia Garcia, MD. *Maternidad Suizo, Buenos Aires, Argentina:* Vanesa DiGruccio, MD; Fernanda Tamanaha, MD. *Sanatorio de la Trinidad, Buenos Aires, Argentina*: Noemí Jacobi, MD. *Sanatorio Otamendi, Buenos Aires, Argentina*: Silvia Garcia, MD; Norma Vivas, MD; Cristina Osio, MD. *Stony Brook University Medical Center, Stony Brook, NY*: Shanthy Sridhar, MD, FAAP; Aruna Parekh, MD; Rose McGovern, RN. *Meir Medical Center, Kfar-Saba, Israel*: Shmuel Arnon, MD; Michelle Meyer, RN; Rachel Poller, RN. *McGill University Health Centre, Montreal, Quebec, Canada:* Nabeel Ali, MD, FRCPC; May Khairy, MD,CM, FRCPC; Isabelle Paquet, PhD; Larissa Perepolkin, BA; Patricia Grier, BScN; Sadia Wali, DMD. *Winnipeg Health Sciences Centre, Winnipeg, Manitoba, Canada*: Mary Seshia, MBChB, MRCP (UK), FRCP(Ed); Diane Moddemann, MD, MEd, FRCP, FAAP; John Minski, RRT; Valerie Cook, RN; Kim Kwiatkowski, RN; Karen A. H. Penner, MSc, BMROT; Debbie Williams, RN, BN. *Royal University Hospital, Saskatoon, Saskatchewan, Canada*: Laurentiu Givelichian, FRCP(C); Koravangattu Sankaran, MD, FRCP, FCCM; Cindy Thiel, MS, RN (NP), NNP-BC. *Bnai Zion Medical Center, Haifa, Israel*: David Bader, MD, MHH; Bella Sandler, RN. *St Boniface General Hospital, Winnipeg, Manitoba, Canada*: Aaron Chiu, MD, FRCPC, FAAP; Diane Moddemann, MD, MEd, FRCP, FAAP; Dayle Everatt, RCT, RN, BA; Naomi Granke, RN, CCRP. *Soroka University Medical Center, Beer Sheva, Israel*: Agneta Golan, MD; Esther Goldstein, PhD; Shlomith Dadoun, BN. *Oulu University Hospital, Oulu, Finland:* Riitta Vikevainen, RN; Hanna Kallankari, MD; Tuula Kaukola, PhD; Mikko Hallman, MD, PhD, FRCPE. *Centre Hospitalier Universitaire Sainte-Justine, Montreal, Quebec, Canada*: Keith Barrington, MB, ChB; Julie Lavoie, RN. *Steering Committee*: Barbara Schmidt (chair), MD, MSc, FRCPC, McMaster University, Hamilton, Ontario, Canada, and University of Pennsylvania, Philadelphia; Elizabeth V. Asztalos, MD, MSc, FRCPC, University of Toronto, Toronto, Ontario, Canada; Christian F. Poets, MD, Eberhard Karls University, Tuebingen, Germany; Yacov Rabi, MD, University of Calgary, Calgary, Alberta, Canada; Robin S. Roberts, MSc, McMaster University, Hamilton, Ontario, Canada; Alfonso Solimano, MD, FRCPC, University of British Columbia, Vancouver, Canada; Robin K. Whyte, MBBS, FRCPC, Dalhousie University, Halifax, Nova Scotia, Canada. *Bayley III Adjudication Committee*: Diane Moddemann, MD, MEd, FRCP, FAAP, University of Manitoba, Winnipeg, Canada; Karen A. H. Penner, MSc, BMROT, University of Manitoba, Winnipeg, Canada. *Data and Safety Monitoring Board*: William Fraser (chair), MD, MSc, University of Montreal, Montreal, Quebec, Canada; Deborah J. Davis, MDCM, CSPQ, FRCPC, University of Ottawa, Ottawa, Ontario, Canada; George Wells, MSc, PhD, University of Ottawa, Ottawa, Ontario, Canada. *Nurse Consultant*: Judy D'Ilario, RN, McMaster University, Hamilton, Ontario, Canada. *Neonatal Trials Group (Coordinating Center) at McMaster University, Hamilton, Ontario, Canada*: Robin S. Roberts, MSc; Lorrie Costantini, BA; Judy D'Ilario, RN; Wendy Yacura; Bronwyn Gent; Harvey Nelson, MSc.

Funding/Support: This study was funded exclusively by Canadian Institutes of Health Research grant MCT-79217.

Role of the Funder/Sponsor: The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

REFERENCES

1. Martin RJ, Wang K, Köroğlu O, Di Fiore J, Kc P. Intermittent hypoxic episodes in preterm infants: do they matter? *Neonatology*. 2011;100(3):303-310.

2. Bolivar JM, Gerhardt T, Gonzalez A, et al. Mechanisms for episodes of hypoxemia in preterm infants undergoing mechanical ventilation. *J Pediatr*. 1995;127(5):767-773.

3. Poets CF. Interventions for apnoea of prematurity: a personal view. *Acta Paediatr*. 2010;99(2):172-177.

4. Schmidt B, Whyte RK, Asztalos EV, et al; Canadian Oxygen Trial Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA*. 2013;309(20):2111-2120.

5. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214-223.

6. Bayley N. *Manual for the Bayley Scales of Infant and Toddler Development*. San Antonio, TX: Psychological Corp; 2006.

7. Section on Ophthalmology, American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2006;117(2):572-576.

8. Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*. 2001;108(2):E35.

9. Di Fiore JM, Kaffashi F, Loparo K, et al. The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants. *Pediatr Res*. 2012;72(6):606-612.

10. Koons AH, Mojica N, Jadeja N, Ostfeld B, Hiatt M, Hegyi T. Neurodevelopmental outcome of

infants with apnea of infancy. *Am J Perinatol*. 1993;10(3):208-211.

11. 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(3):155-161.

12. Levitt GA, Mushin A, Bellman S, Harvey DR. Outcome of preterm infants who suffered neonatal apnoeic attacks. *Early Hum Dev*. 1988;16(2-3):235-243.

13. Cheung PY, Barrington KJ, Finer NN, Robertson CMT. Early childhood neurodevelopment in very low birth weight infants with predischarge apnea. *Pediatr Pulmonol*. 1999;27(1):14-20.

14. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, Barrington KJ. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *J Perinatol*. 2004;24(12):763-768.

15. Esquer C, Claure N, D'Ugard C, Wada Y, Bancalari E. Mechanisms of hypoxemia episodes in spontaneously breathing preterm infants after mechanical ventilation. *Neonatology*. 2008;94(2):100-104.

16. Poets CF, Stebbens VA, Alexander JR, Arrowsmith WA, Salfield SA, Southall DP. Arterial oxygen saturation in preterm infants at discharge from the hospital and 6 weeks later. *J Pediatr*. 1992;120(3):447-454.

17. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893-1902.

18. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.

19. Doyle LW, Schmidt B, Anderson PJ, et al. Reduction in developmental coordination disorder with neonatal caffeine therapy. *J Pediatr*. 2014;165(2):356-359.

20. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112-2121.

21. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev*. 2010;(12):CD000140.

22. Bucher HU, Duc G. Does caffeine prevent hypoxaemic episodes in premature infants? a randomized controlled trial. *Eur J Pediatr*. 1988;147:288-291.

23. Rhein LM, Dobson NR, Darnall RA, et al; Caffeine Pilot Study Group. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. *JAMA Pediatr*. 2014;168(3):250-257.

24. Steer P, Flenady V, Shearman A, et al; Caffeine Collaborative Study Group Steering Group. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(6):F499-F503.

25. Pantalitschka T, Sievers J, Urschitz MS, Herberts T, Reher C, Poets CF. Randomised crossover trial of 4 nasal respiratory support systems for apnoea of prematurity in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4):F245-F248.

26. Poets CF, Darraj S, Bohnhorst B. Effect of doxapram on episodes of apnoea, bradycardia and hypoxaemia in preterm infants. *Biol Neonate*. 1999;76(4):207-213.