Pre-Vent Apnea

ClinicalTrials.gov numbers:
NCTpending *(when available)* for Aim 2
NCTpending *(when available)* for Aim 3

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Contents

SECTION 1. ABSTRACT

Study Objective

Prospectively define and validate ventilatory mechanisms associated with resilience against or risk for development of impaired oxygenation at 36 weeks' postmenstrual age (physiologic definition of BPD) and at follow-up (corrected age of 3 months)

Study Design Type

Aim 1: Prospective Observational Study

Aims 2 and 3: Randomized Cross-over Comparative Effectiveness Trial

Eligibility Criteria

Aim 1: This study will enroll neonates in our Regional NICU (RNICU) at UAB as follows:

Inclusion:

- Inborn infants weighing 401-1,000 grams on admission and/or $22^{0/7}$ to $28^{6/7}$ (<29 weeks) inclusive completed weeks of gestation,
- Infants eligible for full care and resuscitation as necessary, and surviving beyond 24 h of age
- Enrollment at <1 week post-natal age
- Informed consent from parent/guardian

Exclusion

- Refusal or withdrawal of consent
- Major congenital malformations (e.g., not including patent ductus arteriosus, small hernia)

Aim 2: This study will enroll the subset of infants from Aim 1 who are still intubated or on nasal IMV at 2 weeks postnatal age, meet blood gas criteria (arterial or capillary arterialized blood gas values done q12-24h, as most infants do not have an arterial line at 2 weeks: pH >7.25, $PaCO_2$ >40 mm Hg), have $TcCO_2$ monitoring with $TcCO_2$ values that trend and correlate appropriately with $PaCO_2$, and are not judged too unstable by the Attending neonatologist.

Aim 3: This study will enroll the subset of infants from Aim 1 who are receiving oxygen supplementation at 32w and 36w PMA, and are not judged too unstable by the Attending neonatologist.

Study Intervention/Methods

After parental consent is obtained, infants will be enrolled in prospective collection of continuous physiologic data from vital signs monitors (HR, RR, SpO_2). In addition, intensive multiparametric physiologic monitoring and data collection (96 hours each) at three distinct time frames: 2 weeks postnatal age, 32 weeks post-menstrual age (PMA), 36 weeks PMA will be done, along with a sleep study at 36 w PMA and 3 months corrected age. Aim 1 will be observational, using physiological data to develop predictive mathematical models for outcomes. Aim 2 will determine if late (at or beyond postnatal day 14) mild permissive hypercapnia is associated with reduction in apnea, bradycardia, and hypoxemic episodes and with improved stability of oxygenation. Aim 3 will determine if servo-controlled oxygen environment is associated with reduction in hypoxemic episodes and improved stability of oxygenation, as compared to oxygen administered by nasal cannula.

Primary Outcome

Hypoxemic episode (SpO2 <85% for ≥10s) frequency

Secondary Outcome(s)

Frequency of Hypoxemia (SpO_2<85%), Bradycardia (HR<100/min), Bradycardia episode (HR<100/min for ≥10s); Apnea (RR=0 for >20s, or RR=0 for ≥10s + SpO2 <85% or HR<100/min); BPD defined using physiologic definition at 36w PMA

SECTION 2. CONFLICT OF INTEREST DISCLOSURES

Per Title 42, Code of Federal Regulations, Part 50, Subpart F (50.604 Responsibilities of Institutions regarding Investigator financial conflicts of interest), as amended, institutions and all subrecipients are required to notify the grants officer of any financial conflicts of interest (FCOI) prior to expenditure of any funds and within 60 days of any subsequently identified FCOI.

Financial Conflicts of Interest of the Institutions and Investigators
No conflicts of interest exist with commercial entities.

SECTION 3. STATEMENT OF PROBLEM

3.1. PRIMARY HYPOTHESIS OR QUESTION

Aim 1: We hypothesize that mathematical models of personalized ventilatory patterns based on multiparametric vital signs monitoring and signal analysis methods will be able to predict hypoxemic episodes in individual infants before they occur.

Aim 2: We hypothesize that late (at or beyond postnatal day 14) mild permissive hypercapnia is associated with reduction in hypoxemic episodes

Aim 3: We hypothesize that servo-controlled oxygen environment is associated with reduction in hypoxemic episodes, as compared to oxygen administered by nasal cannula

3.2. SECONDARY HYPOTHESIS OR QUESTIONS (S) (IF APPLICABLE)

Aim 1: We hypothesize that mathematical models of personalized ventilatory patterns based on multiparametric vital signs monitoring and signal analysis methods will be able to predict (a) bradycardia events, (b) hypoxemic time, (c) bradycardia time, (d) apneic episodes in individual infants before they occur,

Aim 1: We hypothesize that mathematical models of personalized ventilatory patterns based on multiparametric vital signs monitoring and signal analysis methods will be able to identify patterns of ventilatory abnormalities associated with BPD with and without pulmonary hypertension, as well as with and without respiratory or feeding support at 3 months corrected age.

Aim 2: We hypothesize that late (at or beyond postnatal day 14) mild permissive hypercapnia is associated with reduction in (a) bradycardia events, (b) hypoxemic time, (c) bradycardia time, (d) apneic episodes

Aim 3: We hypothesize that servo-controlled oxygen environment is associated with reduction in (a) bradycardia events, (b) hypoxemic time, (c) bradycardia time, (d) apneic episodes

3.3. BACKGROUND AND RATIONALE

Aim 1:

The respiratory rhythm is initiated by brainstem neural circuits that signal the timing and magnitude of each breath. Preterm infants have irregular breathing due to immaturity of these brainstem circuits. The irregularity in breathing can be quantified by the interbreath interval (IBI), the time interval between breaths, and its variations in time around the mean (the IBI variability) (1, 2). The probability density distribution (P) of IBIs follows a power law, $P(IBI) \sim IBI^{-\alpha}$, with the exponent α indicating the relative risk of insufficient breathing. With maturation, α increases from 2.6 ± 0.4 at 41 ± 4 wk to 3.2 ± 0.4 at 47 ± 6 wk PMA, indicating a decrease in apnea ($p = 0.002$) (1, 2). Analysis of IBI in infants indicates stochastic characteristics (1) as well as deterministic dynamic characteristics (e.g. low frequency oscillations with periodic apnea) (3).

The Analytical Core with Drs. Indic, Paydarfar, and Bloch-Salisbury has pioneered an algorithm to capture both the stochastic as well as deterministic dynamic characteristics of IBI, providing a framework for computing the instantaneous estimates of variability in breathing (2, 4). In this point process model, a lognormal parametric structure represents the stochastic nature of IBI and a higher p-

order autoregressive (AR (p)) model describes the dynamic nature of IBI (2). The descriptors used to study the instantaneous characteristics of IBI include: 1) mean IBI, *M;* 2) variance of IBI, *V;* 3) skewness of IBI, *S;* 4) kurtosis of IBI, *K*; 5) mean respiratory rate, *Mr* ; 6) variance of respiratory rate, *Vr* ; 7) spectrum, and 8) poles. These parameters and descriptors provide an innovative approach for the assessment of instability of breathing in neonates. **Figure 1** illustrates an example of IBI data along with the estimated μ and σ2. It is evident that σ2 shows fast step increases both prior and during the apnea event.

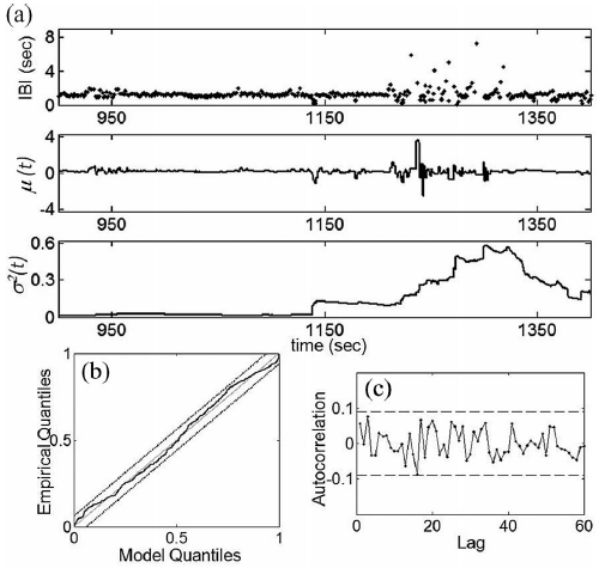

Figure 1: (a) Instantaneous time varying estimated μ and σ2 for the IBI data from a preterm infant with local likelihood window W= 120 s, time step Δt = 0.05, α = 0.01 (optimized by KS analysis), and p = 4 (optimized by AIC, autocorrelation function, and KS analysis). (b) KS plot (black line) of the time-rescaled quantiles derived from the model. (c) Autocorrelation function of the transformed times estimated for the first 60 lags. Dotted lines represent the 95% CI. (From Indic et al. 2013)

Figure 2 indicates how both spectrum and predominant pole provides additional dynamic measures of IBI instability that precede apnea. Kolmogorov-Smirnov (KS) tests and autocorrelation plots indicate that the model is able to accurately capture the stochastic structure. Similar point process models have been developed for bradycardia and its severity. Integrated power spectrum dynamics are larger following apneic episodes, indicating that apnea induces instability in IBI that is maintained for at least several minutes following apnea (which is familiar to clinicians, as one episode of apnea is often followed by others) (**Figure 3**).

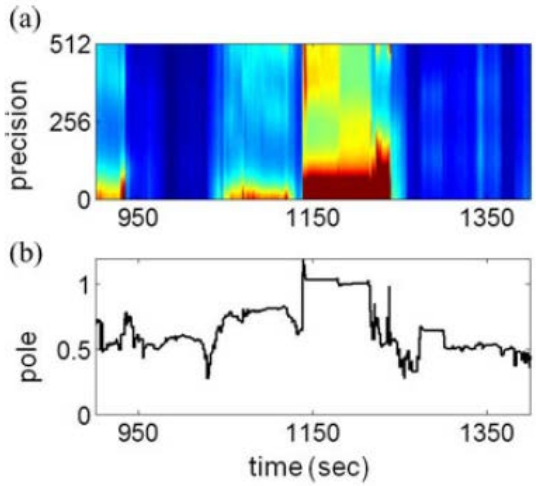

Figure 2: Instantaneous time-varying estimates of spectrum (a) and dynamics of predominant pole (b) of IBI data, for same infants as in Figure 2. (From Indic et al. 2013)

In preterm infants, cardio-respiratory interactions are considered an important indication of the level of maturation of vagally-mediated autonomic effects on the heart, although the exact relationship between heart rate variability (HRV) and respiration in preterm infants has not been determined (5). The influence of respiration on heart rate variability (called "respiratory sinus arrhythmia" or RSA) is detected by a peak in the power spectrum of HRV at the breathing frequency. This signature of RSA occurs normally at the breathing frequency of ~1 Hz (60/min) in a preterm neonate, but may not be observed due to irregularity in breathing. We have developed a new framework for studying the interaction between heart rate variability and respiration in preterm infants (6). We quantified cardio-respiratory interactions in 11 preterm infants using multivariate autoregressive analysis and calculated the coherence as well as gain using causal approaches. The significance of the interactions in each infant

was determined by surrogate data analysis. The method was tested in control conditions as well as in two different experimental conditions; with and without use of mild vibrotactile intervention. Compared to traditional spectral techniques, this bivariate approach considers both the R-R interval and respiratory signal in a single modeling framework and is able to separate the mutually directional causal interactions between RR and respiration. The closed-loop causal formulation quantifies features otherwise not identifiable by standard measures of HRV and allows separation of interactions between RR and respiration occurring in both directions (6). Of note, we found a large percentage of power in the LF (0.01-0.015Hz) range due to pauses in breathing and slow frequency patterns in the respiratory signal. Our finding of a bidirectional interaction between HRV and respiration suggests that fluctuations in cardiac dynamics may also alter respiratory frequency and potentially induce apnea.

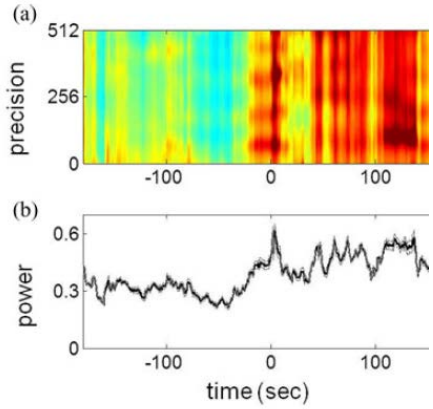

Figure 3. (a) Average power spectrum in a time frequency representation for the IBI data from a preterm infant with apneic episodes. Zero on time axis represents the time of apnea event. (b) Average integrated power (black line) along with the 95% confidence interval (gray line). The average power is significantly different prior and post apnea events with $p < 0.001$ (From Indic et al. 2013).

We have recently shown in a prospective cohort study of 145 ELBW infants that pulmonary hypertension is relatively common, affecting at least 1 in 6 ELBW infants, and persists to discharge in most survivors (7). It is possible that recurrent hypoxemic episodes induce hypoxic pulmonary vasoconstriction and increase the risk of pulmonary hypertension in the setting of BPD. This hypothesis will be rigorously tested in this Aim.

Aim 2:

Abnormal regulation of breathing is the underlying cause of apnea of prematurity. Gerhardt and Bancalari (8) demonstrated more than three decades ago that compared to gestational age, postnatal age and birth weight-matched control infants without apnea, infants with apnea had lower tidal volume (4.4 $\pm$ 1 vs 5.3 $\pm$ 1.6 mL/kg), lower alveolar ventilation (96 $\pm$ 21 v 129 $\pm$ 33 mL/kg/min), higher alveolar PCO_2 (45.4 $\pm$ 8.5 vs 35.6 $\pm$ 4.7 mm Hg), lower esophageal pressure change (4.5 $\pm$ 0.9 vs 6.0 $\pm$ 1.8 cm H_2O), and flatter slope of the CO_2 response curve ($\Delta Ve/\Delta Paco_2$ (20.2 +/- 10.6 vs 40.7 +/- 19.9 mL/min/kg/mm Hg CO_2). This impaired central chemosensitivity is improved by methylxanthines and may account for reduction of apnea by these agents. Importantly, Carlo (UAB Co-Inv) et al. (9) demonstrated in healthy preterm infants using electromyograms (EMGs) and hyperoxic CO_2 rebreathing that the upper airway muscles (e.g. genioglossus and alae nasi) have a higher CO_2 threshold compared to the posterior cricoarytenoid and diaphragm which may contribute to an imbalance between the negative pressure generated by the chest wall muscles and the concomitant upper airway dilation, leading to upper airway collapse and obstructive apnea.

The baseline $PaCO_2$ in both preterm infants is only 1.3 mm Hg above the apneic threshold compared to 3-4 mm Hg for adults (10) and this closeness suggests that small oscillations of $PaCO_2$ in response to carotid body hyperactivity, mild hyperventilation, stimulation, etc may lead to apnea. In preterm infants, eupneic $PaCO_2$ was 38.6$\pm$1 mm Hg, the pre- periodic breathing $PaCO_2$ apneic threshold was 37.3 $\pm$ 1 mm Hg, the post-periodic $PaCO_2$ was 37.2 $\pm$ 1.4 mm Hg, and the transition from eupneic $PaCO_2$ to $PaCO_2$ apneic threshold preceding periodic breathing was accompanied by a small increase in breathing frequency (10).

Lung injury may be reduced by reducing volutrauma by a strategy of minimal ventilation and tolerance of higher $PaCO_2$. We have shown earlier that a ventilatory strategy of mild permissive hypercapnia ($PaCO_2$ 45-55 mm Hg) compared to normocapnia (35-45 mm Hg) is associated with fewer very preterm infants on assisted ventilation during the first 96 hours after randomization, and without differences in mortality, air leaks, intraventricular hemorrhage, PDA or other complications (11). On the other hand, evaluation of a higher $PaCO_2$ target of 55-65 mm Hg compared to 35-45 mm Hg during the first 7 postnatal days suggested that clinical outcomes were not improved with the hypercapnia maybe because the duration or magnitude of hypercapnia were not sufficient (12).

In the SAVE study, to determine whether minimal ventilation (PCO_2 target >52 mm Hg) decreased death or BPD, compared to routine ventilation (PCO_2 target <48 mm Hg), preterm infants (birth weight 501-1000g) and mechanically ventilated before 12h were randomly assigned to either minimal or routine ventilation strategies, along with a tapered dexamethasone course or placebo for 10 days, using a 2x2 factorial design (13). After enrollment of 220 patients, the trial was halted because of nonrespiratory adverse events related to dexamethasone (spontaneous intestinal perforation). Despite the early termination of the trial, an important finding was that ventilator support at 36 weeks was 1% in the minimal versus 16% in the routine group (p <0.01). However, there was no difference in BPD/death at 36w (RR 0.93, 95% CI 0.77-1.12, p=0.43) due to the inclusion of moderate BPD and death in the outcome (13).

More recently, in SUPPORT comparing CPAP and a protocol-driven limited ventilation strategy to early intubation, surfactant and conventional ventilation strategy, infants in the CPAP group had extubation criteria that included a PaCO2 <65 mm Hg with pH>7.2 (14). On the other hand, the surfactant group had extubation criteria that included a PaCO2 <50 mm Hg with pH>7.3 (14). The primary outcome of death or physiological BPD at 36w PMA was not significantly different, but better secondary outcomes were noted in the CPAP group (e.g. lower mortality in the 24-25w pre-specified subgroup, fewer days of mechanical ventilation, less postnatal steroids) (14). However, apnea and instability in oxygenation were not specifically evaluated in this trial. We performed a secondary analysis of $PaCO_2$ in relation to outcome in SUPPORT, and observed that severe IVH, BPD, and neurodevelopmental impairment were associated with hypercapnic infants (maximum $PaCO_2$ in the highest quartile) and fluctuators (infants with both hypercapnia and hypocapnia – with maximum $PaCO_2$ in highest quartile and minimum $PaCO_2$ in lowest quartile) (15). Maximum $PaCO_2$ was positively correlated with maximum FiO_2 (r_s 0.55, p<0.0001) and ventilator days (r_s 0.61, p<0.0001), generally considered markers of illness severity, suggesting that high $PaCO_2$ is a surrogate marker for respiratory illness severity (15). Of interest, the average $PaCO_2$ even in infants without severe IVH was ≥48 mm Hg in the first two postnatal weeks with a relatively narrow IQR (~10 mm Hg). Our data suggest clinical practices have evolved to maintain $PaCO_2$ in the 'permissive hypercapnia' range (45–55 mm Hg)(15).

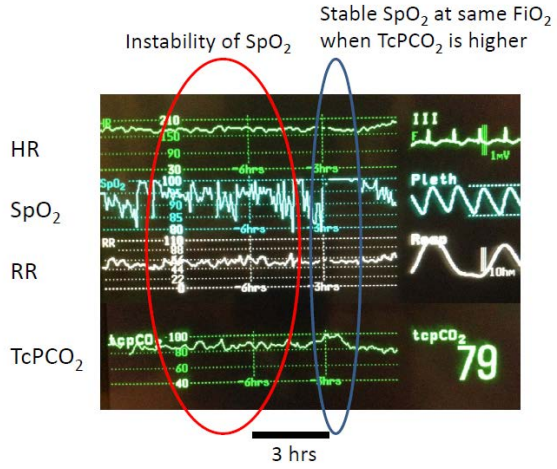

Figure 4: Trend view of heart rate (HR), oxygen saturation (SpO_2), respiratory rate (RR), and transcutaneous PCO_2 ($TcPCO_2$;~15 mmHg above $PaCO_2$ in this infant) in a 2 week old preterm infant on low SIMV settings (rate 25, 15/4, FiO_2 0.21-0.25). SpO_2 was more stable when the $TcPCO_2$ was higher. Note marked fluctuation in SpO_2, and normal variability in HR, RR, and $TCPCO_2$.

A current gap in our knowledge is whether maintenance of PCO_2 at a higher level during the period of maximum risk of apnea after the first week or two (when the theoretical risk of IVH due to higher $PaCO_2$ has also resolved) will keep the $PaCO_2$ above the apneic threshold PCO_2 (that is normally only 1 mm Hg below the baseline $PaCO_2$)(10) and lower the rate of apnea. Mild permissive hypercapnia may elevate the $PaCO_2$ sufficiently above the apneic threshold, improving stability of oxygenation. In our NICU, we frequently observe on trend analysis (12-hour trend view is standard, along with waveform and real-time values) that infants have fewer apnea and desaturations when they have a higher TcPCO2 (**Figure 4**) but this phenomenon has not been systematically investigated.

Aim 3:

The goal of oxygen supplementation is to maintain stability of oxygenation, i.e., adequate oxygenation while minimizing episodes of hypoxemia and hyperoxemia. Preterm infants have respiratory instability which makes it challenging to target oxygen saturation in the desired range (16). As a consequence, preterm infants spend a considerable proportion of time outside (usually higher than) the targeted range (17). While avoiding hypoxemia is important, hyperoxemia can lead to oxidative injury. Intermittent hypoxemia in preterm infants is associated with episodic spontaneous transient hypoventilation. Caregivers often increase FiO_2 during these episodes that may result in hyperoxemia, leading to a pattern of intermittent hypoxemia alternating with hyperoxemia.

intermittent hypoxemic episodes are associated with worse short-term (e.g. increased respiratory support, retinopathy of prematurity, and time to full feeds)(18) and longer-term outcomes (e.g. neurodevelopmental impairment or NDI)(16). Using data from a subset of 115 preterm infants enrolled in the SUPPORT trial, Di Fiore et al.(19) found that infants randomized to the lower SpO_2 target range (85-89%) had more episodes of intermittent hypoxemia [defined as ≤ 80 % for ≥ 10 seconds and ≤ 3 minutes] in the 12 days after birth and beyond 57 days after birth compared to infants randomized to the higher oxygen saturation (91-95%) target range [$p < 0.05$]. These episodes became shorter in duration but increased in severity with increasing postmenstrual age in both groups. Di Fiore et al. (18) had previously found that hypoxemic episodes are common [50-100/day] in infants at the lowest gestations and increase until 6 weeks after birth, followed by a decrease in weeks 6 through 8.

Target oxygen saturations at UAB are based on data from the meta-analysis of randomized controlled trials of oxygen saturation targets which included data on 4911 infants from the SUPPORT, COT, and BOOST II trials (20). Targeting higher SpO_2 [91-95%] increased the risk of severe retinopathy of prematurity [RR 0.74; 95 % CI, 0.59-0.92] while targeting lower SpO_2 [85-89 %] increased the risk of death [1.41; 95 % CI 1.14-1.74] and necrotizing enterocolitis [RR 1.25; 95 % CI 1.05-1.49](20). Rates of BPD [RR 0.95; 95 % CI, 0.86-1.04] or other outcomes were not different between groups. Therefore, the higher oxygen saturation target (91-95% or 90-95% based on expert recommendations) is used at UAB.

A prospective study followed 71 premature infants < 1500 g receiving O_2 until they reached 31 weeks' PMA (21). Infants on nasal cannulae spent more time above the target range compared to infants on NIPPV/CPAP [Mean ± SD, 60 ± 14 v 41 ± 17%; $p<0.002$] indicating that O_2 delivery modes may affect SpO_2 targeting. O_2 delivery at flows ≤ 1 liter through nasal cannulae, although common, is relatively unstudied and many infants receive an effective FiO_2 <0.23 (22). Nasal cannulae allow entrainment of air with infant breaths (23, 24). The effective hypopharyngeal fraction of inspired O_2 [FiO_2] can be calculated using formulae incorporating FiO_2, cannula flow, and minute ventilation (24-27). However, effective O_2 concentration is affected by the magnitude of mouth breathing as well as fluctuations in breathing rate, volume, and inspiratory time (28). At our NICU, the incubators are fitted with a servo-controlled system (Giraffe incubator with a Servo Control Oxygen System and Giraffe Omnibed) for inspired O_2 administration that we have termed "oxygen environment". Oxygen is pumped into the incubator and titrated to a set FiO_2 via servo-control. This mode of O_2 supplementation

may provide a more stable SpO_2 in preterm infants that are receiving O_2 therapy compared to nasal cannulae but this hypothesis has not been rigorously tested.

Oxygen environment avoids the difficulty of needing to calculate effective O_2 concentrations as the set O_2 concentration is equal to the hypopharyngeal O_2 concentration and there is no change in hypopharyngeal O_2 concentration with mouth breathing or with fluctuations in respiratory effort. Oxygen environment and nasal cannulae are both commonly used methods of O_2 delivery at UAB and worldwide. If one method is found to be more effective at maintaining the stability of oxygen saturations and decreasing episodes of intermittent hypoxemia this will be an important clinical finding.

SECTION 4. METHODS

4.1. STUDY POPULATION

4.1.1. Inclusion Criteria

This study will enroll 120 neonates in our Regional NICU (RNICU) at UAB as follows:

1. Inborn infants weighing 401-1,000 grams on admission and/or $22^{0/7}$ to $28^{6/7}$ (<29 weeks) inclusive completed weeks of gestation,
2. Infants eligible for full care and resuscitation as necessary, and surviving beyond 24 h of age
3. Enrollment at <1 week post-natal age
4. Informed consent from parent/guardian

Aim 2: This study will enroll the subset of infants from Aim 1 who are still intubated or on nasal IMV at 2 weeks postnatal age, meet blood gas criteria (arterial or capillary arterialized blood gas values done q12-24h, as most infants do not have an arterial line at 2 weeks: pH >7.25, $PaCO_2$ >40 mm Hg), have $TcCO_2$ monitoring with $TcCO_2$ values that trend and correlate appropriately with $PaCO_2$, and are not judged too unstable by the Attending neonatologist.

Aim 3: This study will enroll the subset of infants from Aim 1 who are receiving oxygen supplementation at 32w and 36w PMA, and are not judged too unstable by the Attending neonatologist.

4.1.2. Exclusion Criteria

1. Refusal or withdrawal of consent
2. Major congenital malformations (e.g., not including patent ductus arteriosus, small hernia)

4.2. DETAILED STUDY PROCEDURES

4.2.1. Screening

Clinical research coordinators will screen very preterm infants admitted to the neonatal intensive care unit for meeting inclusion criteria

4.2.2. Consent Procedures

Consent will be obtained after birth of the infant (postnatal consent) at <1 week postnatal age, using IRB-approved informed consent forms, by the clinical research coordinator or PI/designee.

4.2.3. Randomization Procedures

Aim 1: No randomization – this is an observational study on all enrolled infants

Aim 2: Infants enrolled in Aim 2 will be randomized using a computer-generated random sequence generator to either (a) initially increase TcCO2 by 5 mmHg above baseline (max of 70 mm Hg; as long as pH >7.25) or (b) initially decrease TcCO2 by 5 mmHg below baseline (minimum of 40 mm Hg)

Aim 3: Infants enrolled in Aim 3 will be randomized using a computer-generated random sequence generator to either (a) initially administer oxygen by servo-controlled oxygen environment, or (b) initially administer oxygen by nasal cannula

4.2.4. Study Intervention and Comparison

Aim 1:

This is a non-interventional observational study, in which we will use the data from the intensive multiparametric physiologic monitoring of 96 hour duration at each of the three time points of 2 weeks postnatal age, 32 weeks PMA, and 36 weeks PMA as well as the polysomnography at 36w PMA and 3 months follow-up for this Aim. In addition, we will use a random sampling (3 continuous h/day of 2 days (Mon/Thurs) in each week of the infant's hospital stay) of the continuous data recording of HR, RR, and SpO_2 from enrollment to discharge. These data will be combined with clinical data during the hospital course as well as during follow-up, specifically data on respiratory or feeding support.

Data used will include HR, RR, SpO_2, ventilator/O_2 supplementation, $P_{ET}CO_2$ (end tidal CO_2 by microcapnography), T_cCO_2 (transcutaneous CO_2), r_cSO_2 (near-infrared cerebral oximetry), r_sSO_2 (near-infrared somatic oximetry), and temperature. Data acquisition, band-pass filtering, and wavelet transforms of the signals will be done as described (2, 4, 6, 29).

We will develop mathematical models of ventilatory patterns to predict apneic, hypoxemic and/or bradycardic episodes in individual infants before they occur. We will quantify the irregularity in breathing using the IBI and IBI variability as defined earlier (2, 4). The normal IBI is around 1 second, but due to the irregular breathing pattern in preterm infants, this may vary from <1s to 20s or longer. For this study, we will define eupnea as IBI $\leq$2s and apneic range as IBI>5s as done previously (29). The basic assumptions of the point process model for breathing are that peak inspiration (maximal inspiratory effort as recorded non-invasively) is a discrete event marked by neuronal inspiratory burst and that IBI dynamics are governed by multiple feedback and feed-forward loops modulating the respiratory oscillator. In addition to the respiratory signal, we will develop models using the ECG and SpO_2 signals plus respiratory signals to determine if accuracy is improved. We have developed point process models for the evaluation of bradycardia and its severity.

Aim 2:

(a) We will use the data from the 96 hours of intensive multiparametric physiologic monitoring at 2 weeks postnatal age. The first 24h of the data collection will be the baseline data. Over the next 72h, we will evaluate 3 interventions in a cross-over manner, with the initial intervention randomly assigned (computer-generated): Intervention 1 (24-48h of data), Intervention 2 (48-72h), and Intervention 3 (72-96h). For example, Intervention 1 may be to increase $TcCO_2$ by 5 mm Hg above baseline (at the time of capillary blood gas) and maintain at that level (by reducing IMV rate or pressures, by clinician decision) for 24h, and Intervention 2 will be to decrease $TcCO_2$ by 5 mm Hg back to initial values (by increasing IMV rate or pressures, by clinician decision) for the next 24h. Intervention 3 will be to repeat Intervention 1 (to increase $TcCO_2$ by 5 mm Hg) to validate that results of Intervention 1 are due to increased PCO_2 and less likely to be random fluctuations. On the other hand, if Intervention 1 is to decrease

$TcCO_2$ by 5 mm Hg (from baseline at time of capillary blood gas) and maintain at that level (by increasing IMV rate or pressures) for 24h, and Intervention 2 will be to increase $TcCO_2$ by 5 mm Hg back to initial values (by decreasing IMV rate or pressures) for the next 24h. Intervention 3 will be to repeat Intervention 1. These interventions are chosen so that we will be able to evaluate the effects of altering $PaCO_2$ on respiratory irregularity while maintaining the pH at or above 7.2, generally regarded as a safe threshold. At the conclusion of interventions and data collection, infants will be managed according to the Clinician's preference.

Aim 3:

For infants on oxygen supplementation at 32w PMA, we will use the data from the 96 hours of intensive multiparametric physiologic monitoring at 32w PMA. For infants on oxygen supplementation at 36w PMA, we will use the 96 hours of intensive multiparametric physiologic monitoring at 36w PMA as well as data from the sleep study

(b) The first 24h of the data collection will be the baseline data. Over the next 72h, we will evaluate 3 interventions in a cross-over manner: Intervention 1 (24-48h of data), Intervention 2 (48-72h), and Intervention 3 (72-96h). Initial intervention will be by random assignment (computer-generated). For example, Intervention 1 may be to switch the infant to the servo-controlled O_2 environment at a range necessary to maintain the optimal SpO_2 (91-95%). As this may not be the same FiO_2 as that by cannula, we will calculate the effective hypopharyngeal FiO_2 using formulae incorporating FiO_2, cannula flow, and minute ventilation (24-27) and adjust from this FiO_2. The first 12h will be for identifying the appropriate FiO_2 and stabilizing tracings, and the second 12 h will be data collected for analysis. Intervention 2 will be then be switching the infant back to the cannula at the FiO_2 and flow rate the infant was receiving in the first 24h (unless the FiO_2 or clinical status had markedly changed in the previous 24h and adjustments are necessary), with analysis of data in the second 12h after stabilization. Intervention 3 will be switching back to the servo-controlled O_2 environment for 24h. Similarly, for infants for whom Intervention 1 is switching to a cannula, Intervention 2 will be back to the O_2 environment, and Intervention 3 back to the cannula. At the conclusion of interventions and data collection, infants will be managed according to the Clinician's preference.

4.2.5. Blinding/Masking

This is an unmasked study.

4.2.6. Control or Monitoring of Co-interventions

Medical interventions and ventilator management will be based upon clinician discretion. Evidence and consensus based guidelines are followed for uniformity in practice. No changes in management are required for this observational cohort study, except for the duration of the intensive multiparametric monitoring for 96 hours at 2 weeks postnatal age, 32 weeks PMA, and 36 weeks PMA, when interventions will be performed as described in Aims 2 (minor changes in TcCO2) or Aim 3 (Nasal cannula or Servo-controlled O2 environment).

4.2.7. Primary Outcome

Hypoxemic episodes (defined as SpO2 <85% for ≥10s) will be determined by analysis of stored physiologic data.

4.2.8. Secondary Outcomes *(if applicable)*

1. Hypoxemia defined as SpO2 <85%
2. Bradycardia defined as HR <100/min
3. Bradycardic episode as HR <100/min for ≥10s
4. Apnea defined as RR=0 for >20s, or RR=0 for ≥10s + SpO2 <85% or HR <100/min
5. BPD defined using physiologic definition at 36w PMA

4.2.9. Additional Safety Outcomes *(if applicable)*

Infants will be monitored for severe apnea/bradycardia episodes (defined as requiring bag and mask ventilation for >30 s or chest compression) associated with interventions in Aims 2 and 3. No such episodes were found to be associated with the interventions in pilot studies.

4.2.10. Compliance Monitoring

No specific protocol exists for Aim 1 (observational study). The PI or Research Coordinator or designee will initiate/stop or personally supervise the interventions in Aims 2 and 3. In pilot studies of interventions used in Aims 2 and 3, no issues with maintenance of compliance were noted.

4.2.11. Study Specimens

No biofluid specimens are required for the single-center study, but will be considered in the multicenter protocol.

4.2.12. Post-hospital Procedures

Reminder for follow-up and instructions for follow-up at 3 months will be sent to parents/caregivers.

4.2.13. Follow-up at 3 Months

Survivors to discharge will be followed-up at the 3 month follow-up visit for a sleep study (polysomnographic study) at the Children's of Alabama sleep center by the Pediatric pulmonologist. Respiratory outcomes as in SUPPORT Breathing Outcomes study (30) will be evaluated at the 3 month follow-up visit in addition to the Sleep study.

4.2.14. Additional Follow-up Assessments

This will be decided upon by regular clinical team. Most infants enrolled in this study are eligible for follow-up by the Newborn Follow-Up clinic, and some are also eligible for follow-up by the BPD follow-up clinic.

4.3. POTENTIAL RISKS AND BENEFITS TO SUBJECTS

Potential Risks:

This study is primarily an observational study (Aim 1), and comparative effectiveness research (Aims 2 and 3), and is hence of low risk. Infants enrolled in this study are intrinsically at high risk, as they are born extremely preterm with a risk of death exceeding 20% and death or disability exceeding 50%, but participation in this study adds only minimally to the underlying risk.

For Aim 1, we will collect physiologic data from patient monitors, and clinical data on patient characteristics, illness severity, and outcomes from the medical records of the 120 enrolled infants. The primary risks are those of loss of confidentiality and privacy. Results and their linked clinical data will then be assigned an unique identifying code and anonymized to minimize risks to confidentiality. Only the PI and research coordinator will have access to patient data before anonymization. No patient identifiers will therefore remain in the data set that will be transmitted to the Data Coordinating Center.

For Aim 2, we will enroll a subset of infants from Aim 1 to determine if mild permissive hypercapnia (trying to increase blood carbon dioxide concentrations 5 mm Hg from baseline) leads to improved control of breathing in preterm infants. While extreme hypercapnia associated with pH <7.15 is generally avoided, mild hypercapnia with pH maintained >7.2 is usual practice in most centers, including UAB, and is considered safe. These infants will be monitored using continuous pulse oximetry and transcutaneous CO_2 monitoring, and the fluctuations in blood carbon dioxide concentrations of 5 mm Hg from baseline are expected to alter blood pH by less than 0.05, and these fluctuations are much less than normally noted in routine care (fluctuations of up to 30 mm Hg or more over a day are often seen). We will not include infants with extreme blood carbon dioxide concentrations (blood PCO_2 of less than 40 mm Hg or more than 70 mm Hg as indicated by transcutaneous monitoring, after adjustment for skin-blood PCO_2 difference on most recent blood gas analysis). This Aim is intent-to-treat, and it is possible that we will not see any statistical differences over time with regards to blood carbon dioxide concentrations despite our intent to increase or decrease the level by 5 mm Hg, as there are large fluctuations in routine care, due to inherent variation in respiratory drive and other clinical variables. Even more extreme transient elevations of blood carbon dioxide at 2 weeks of age are unlikely to cause clinical problems as the risk period of IVH (the main concern with elevated blood carbon dioxide in preterm infants) is mainly in the first few days after birth. Hypocapnia or very low blood carbon dioxide concentrations may reduce brain blood flow, but we are evaluating infants with levels in the upper end of the normocapnia range or mild permissive hypercapnia, and excluding infants with more extreme values. Infants with hypocapnia generally have spontaneous hyperventilation rather than due to clinician intervention, as the goal is minimal ventilation and not overventilation.

For Aim 3, we will evaluate the effects of oxygen administration using a servo-controlled oxygen environment as compared to nasal cannula on control of breathing and stability of blood oxygen levels. Both methods are in common use in our NICU, and are not known to have any major risks. Minor risks of using a nasal cannula include accidental dislodgement with movement of the infant. Minor risks of oxygen environment include a drop in oxygen concentration if caregivers leave port-holes open for too long by accident, allowing the oxygen to exit the incubator. However, as infants are being carefully monitored using continuous pulse oximetry and ECG monitoring, any desaturation or bradycardia episode will immediately lead to an audible and visible alarm.

We also plan to develop a biorepository using remnant samples, as required by the multicenter collaborative (no invasive sampling will be done specifically for this study).

There is no financial risk from participation in this study.

A potential risk is of psychological harm to parents during the informed consent process, as they become aware of the high risk of death or handicap to their very preterm infant. However, this risk is the same, whether or not the parents are in the study, as they all receive counseling regardless of being in this or other studies.

Risk:	**Frequency**	**Severity**	**Reversibility**
1. Loss of confidentiality and privacy	Very low (anonymized data)	Low	Not applicable

2. Mild increases or decreases in PCO2 Common (happens often routinely) Low Reversible
3. Nasal cannula dislodgement Common (happens often routinely) Low Reversible
4. Oxygen environment open to air Common (happens often routinely) Low Reversible
5. Psychological harm to parents Common (all parents at risk) Low Not applicable

This study is an observational study (Aim 1) and comparative effectiveness study (Aims 2 and 3), and the risks that the infants are exposed to are those that are normally present and happen often in usual neonatal intensive care. As this study involves more intensive monitoring than usual, the expectation is that these infants will be at even lower risk as compared to infants who are monitored only using standard equipment. The minor risks in Aims 2 and 3 occur frequently in infants during usual intensive care, and are likely to be unchanged in this study compared to usual care, but harm may occur if nursing staff do not respond to monitoring alarms (as in usual care). The more intensive monitoring may help reduce these risks.

Potential benefits:

There is a potential of direct benefit to study participants from participating as Aim 1 is based on intensive multi-parametric monitoring of multiple variables only some of which are routinely monitored. As the monitoring is not masked to caregivers, nurses and clinicians may become aware of changes in the monitored variables and intervene more quickly for abnormal cardiorespiratory events and prevent apnea or bradycardia duration in the infants who are enrolled and being monitored, as compared to infants who are not enrolled.

Aims 2 and 3 are comparative effectiveness research studies done in a cross-over fashion, so infants are not likely to have a persistent benefit from one intervention. If caregivers note that one intervention seems to be associated with better oxygen saturation stability, fewer apneic episodes etc, it is possible that these infants may benefit by the better intervention being used after the period of evaluation for Aim 2 or 3.

The results of this study will be published in the peer-reviewed literature and then deposited in PubMed Central to make the manuscript freely available, which may benefit other investigators in the field as well as interested parents and family.

Development and validation of mathematical models of personalized ventilatory patterns based on multiparametric vital signs monitoring and signal analysis methods will enable the scientific community to gain greater insight into the pathogenesis of respiratory disorders in extremely preterm infants and discover targets for new prevention and treatment strategies to improve outcomes for very vulnerable children at the beginning of life

SECTION 5. ANALYTICAL PLAN

5.1. STATISTICAL ANALYSIS PLAN

It should include a plan for analysis of primary and secondary outcomes, subgroup analyses if planned, and for handling of missing data and subjects who die or are lost to follow-up.

Primary Outcome:

Hypoxemic episode (SpO2 <85% for ≥10s) frequency

Secondary Outcome(s)

Frequency of Hypoxemia (SpO_2<85%), Bradycardia (HR<100/min), Bradycardia episode (HR<100/min for ≥10s); Apnea (RR=0 for >20s, or RR=0 for ≥10s + SpO2 <85% or HR<100/min); BPD defined using physiologic definition at 36w PMA

Aim 1: Statistical calculations will be performed using SPSS. Parametric tests will be used for analyses of all continuous variables except for comparisons involving the incidences of specified ranges of IBIs, which is a skew distribution. Nonparametric tests will also be used for analyses of ordinal datasets. The Kolmogorov-Smirnov (one-sample) and Friedman's and Wilcoxon signed-rank tests will be used for the nonparametric analyses. For factorial analyses of parametric data, separate repeated-measures ANOVAs will be used. For factors with more than two levels, the Greenhouse-Geisser correction will be used, and ε with unadjusted degrees of freedom will be reported. Where a main effect was observed for factors with more than two levels, *post hoc* tests using the Bonferroni adjustment will be done. Values will be expressed as means and SD, and *p* values (2-tailed) of <0.05 considered statistically significant. Pearson product-moment correlation coefficient analysis will be used to establish the association between pathological pauses in breathing and breathing stability.

Aims 2 and 3: As in Aim 1, we will quantify IBI and IBI variability as defined earlier (2, 4). Also as in Aim 1, other outcomes will include (i) hypoxemic time –the % time with SpO_2 <90%, (ii) moderate hypoxemic time with SpO_2 <80% and severe hypoxemic time with SpO_2 <60% (iii) bradycardic time – % time with HR <100, (iv) severe bradycardic time – % time with HR <60, (iv) hypoxemic, bradycardic, or apneic episodes – the number of episodes of SpO_2 <90%, SpO_2 <80%, SpO_2 <60%, HR<100, HR<60, or RR=0, respectively, for >10 seconds, with the episode length defined as the number of seconds of data values below the threshold, (v) cerebral hypoxemic episodes (decrease in r_cSO_2 <50% or of 20% from baseline for >1 minute) and somatic hypoxemic episodes (decrease of 20% from baseline in peri-renal area).

5.2. SAMPLE SIZE AND POWER ESTIMATES

Aim 1: A sample size of 100 infants per group is sufficient to detect a 20% change in a parameter related to an outcome using standard parametric or nonparametric tests (e.g. Wilcoxon signed-rank) at 80% power, α=0.05, with expected standard deviation of change of 50%. We plan to enroll 120 to account for attrition due to early death. Statistical power of 80% for detecting 20% difference in parameters is maintained even if the incidence of outcome (e.g. BPD) is only 20% of enrolled (24 of 120) infants if the standard deviation is 40% or less (as is expected to be, based on preliminary studies).

Aim 2: A sample size of 16 infants is sufficient to detect a 30% change in a parameter related to an outcome using standard parametric (e.g. paired t-test) or nonparametric tests at 80% power, α=0.05, with expected standard deviation of change of 40%. Hence, enrollment of 25 patients will be sufficient, even if there is attrition of up to 5 patients due to death, and data from 4 patients has technical issues with usability.

Aim 3: As in Aim 2, 16 infants are sufficient to detect a 30% change in a parameter related to an outcome by standard parametric (e.g. paired t-test) or nonparametric tests at 80% power, α=0.05, with expected standard deviation of 40%. Hence, enrollment of 25 patients will enable detection of even minimal changes, or of changes in parameters with much variation.

5.3. AVAILABLE POPULATION

We have an estimated available population of 200 extremely preterm infants each year admitted to the RNICU. The limitation of sample size to 120 is due to costs associated with study (NIRS sensors, sleep studies) rather than with limitation in the number of available infants.

5.4. PROJECTED RECRUITMENT TIME

We plan to enroll at least 40 infants per year during years 2-4 of the study (120 in total), with additional enrollment possible in early Year 5. As infants will require a sleep study 3 months post-discharge, we will cease enrollment by mid-Year 5 to ensure all infants have all necessary data available by end of study funding in end-Year 5.

5.5. STUDY MONITORING PLAN

Study monitoring plan is as reported in plan submitted to OSMB, and will be consistent with monitoring at all study centers for adverse events. SAEs will be reported to OSMB and IRB as required. Aim 1 is primarily observational, and Aims 2 and 3 are comparative effectiveness studies evaluating interventions that are routinely used in the NICU. No SAEs attributable to the study interventions are hence anticipated, or have been noted in preliminary studies, even though study monitoring is in place.

SECTION 6. REFERENCES

1. Frey U, Silverman M, Barabasi AL, Suki B. Irregularities and power law distributions in the breathing pattern in preterm and term infants. Journal of applied physiology. 1998;85(3):789-97. Epub 1998/09/08. PubMed PMID: 9729549.
2. Indic P, Paydarfar D, Barbieri R. A point process model of respiratory dynamics in early physiological development. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference. 2011;2011:3804-7. Epub 2012/01/19. doi: 10.1109/IEMBS.2011.6090771. PubMed PMID: 22255168; PubMed Central PMCID: PMC3340562.
3. Waggener TB, Frantz ID, 3rd, Stark AR, Kronauer RE. Oscillatory breathing patterns leading to apneic spells in infants. Journal of applied physiology: respiratory, environmental and exercise physiology. 1982;52(5):1288-95. Epub 1982/05/01. PubMed PMID: 7096153.
4. Indic P, Paydarfar D, Barbieri R. Point process modeling of interbreath interval: a new approach for the assessment of instability of breathing in neonates. IEEE transactions on bio-medical engineering. 2013;60(10):2858-66. Epub 2013/06/07. doi: 10.1109/TBME.2013.2264162. PubMed PMID: 23739777; PubMed Central PMCID: PMC4278369.
5. Rosenstock EG, Cassuto Y, Zmora E. Heart rate variability in the neonate and infant: analytical methods, physiological and clinical observations. Acta Paediatr. 1999;88(5):477-82. Epub 1999/07/30. PubMed PMID: 10426164.
6. Indic P, Bloch-Salisbury E, Bednarek F, Brown EN, Paydarfar D, Barbieri R. Assessment of cardio-respiratory interactions in preterm infants by bivariate autoregressive modeling and surrogate data analysis. Early human development. 2011;87(7):477-87. Epub 2011/04/23. doi: 10.1016/j.earlhumdev.2011.04.001. PubMed PMID: 21511413; PubMed Central PMCID: PMC3114161.
7. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics. 2012;129(3):e682-9. Epub 2012/02/09. doi: 10.1542/peds.2011-1827. PubMed PMID: 22311993; PubMed Central PMCID: PMC3289526.
8. Gerhardt T, Bancalari E. Apnea of prematurity: I. Lung function and regulation of breathing. Pediatrics. 1984;74(1):58-62. Epub 1984/07/01. PubMed PMID: 6429625.
9. Carlo WA, Martin RJ, Difiore JM. Differences in CO2 threshold of respiratory muscles in preterm infants. Journal of applied physiology. 1988;65(6):2434-9. Epub 1988/12/01. PubMed PMID: 3145932.
10. Khan A, Qurashi M, Kwiatkowski K, Cates D, Rigatto H. Measurement of the CO2 apneic threshold in newborn infants: possible relevance for periodic breathing and apnea. Journal of applied physiology. 2005;98(4):1171-6. Epub 2005/03/18. doi: 10.1152/japplphysiol.00574.2003. PubMed PMID: 15772056.
11. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics. 1999;104(5 Pt 1):1082-8. Epub 1999/11/05. PubMed PMID: 10545551.

12. Thome UH, Carroll W, Wu TJ, Johnson RB, Roane C, Young D, et al. Outcome of extremely preterm infants randomized at birth to different PaCO2 targets during the first seven days of life. Biology of the neonate. 2006;90(4):218-25. Epub 2006/04/26. doi: 10.1159/000092723. PubMed PMID: 16636534.
13. Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, Shankaran S, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr. 2002;141(3):370-4. Epub 2002/09/10. PubMed PMID: 12219057.
14. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970-9. Epub 2010/05/18. doi: 10.1056/NEJMoa0911783. PubMed PMID: 20472939; PubMed Central PMCID: PMC3071534.
15. Ambalavanan N, Carlo WA, Wrage LA, Das A, Laughon M, Cotten CM, et al. PaCO2 in surfactant, positive pressure, and oxygenation randomised trial (SUPPORT). Arch Dis Child Fetal Neonatal Ed. 2015;100(2):F145-9. Epub 2014/11/27. doi: 10.1136/archdischild-2014-306802. PubMed PMID: 25425651; PubMed Central PMCID: PMC4336211.
16. Martin RJ, Wang K, Koroglu O, Di Fiore J, Kc P. Intermittent hypoxic episodes in preterm infants: do they matter? Neonatology. 2011;100(3):303-10. Epub 2011/10/12. doi: 10.1159/000329922. PubMed PMID: 21986336; PubMed Central PMCID: PMC3252018.
17. Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. Pediatrics. 2006;118(4):1574-82. Epub 2006/10/04. doi: 10.1542/peds.2005-0413. PubMed PMID: 17015549.
18. 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(1):69-73. Epub 2010/03/23. doi: 10.1016/j.jpeds.2010.01.046. PubMed PMID: 20304417; PubMed Central PMCID: PMC4428609.
19. 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(6):1047-52. Epub 2012/06/29. doi: 10.1016/j.jpeds.2012.05.046. PubMed PMID: 22738947; PubMed Central PMCID: PMC3730286.
20. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014;105(1):55-63. Epub 2013/11/20. doi: 10.1159/000356561. PubMed PMID: 24247112.
21. Arawiran J, Curry J, Welde L, Alpan G. Sojourn in excessively high oxygen saturation ranges in individual, very low-birthweight neonates. Acta Paediatr. 2015;104(2):e51-6. Epub 2014/10/17. doi: 10.1111/apa.12827. PubMed PMID: 25319771.
22. Walsh M, Engle W, Laptook A, Kazzi SN, Buchter S, Rasmussen M, et al. Oxygen delivery through nasal cannulae to preterm infants: can practice be improved? Pediatrics. 2005;116(4):857-61. Epub 2005/10/04. doi: 10.1542/peds.2004-2411. PubMed PMID: 16199694.
23. St Clair N, Touch SM, Greenspan JS. Supplemental oxygen delivery to the nonventilated neonate. Neonatal network : NN. 2001;20(6):39-46. Epub 2002/07/30. doi: 10.1891/0730-0832.20.6.39. PubMed PMID: 12144117.

24. Vain NE, Prudent LM, Stevens DP, Weeter MM, Maisels MJ. Regulation of oxygen concentration delivered to infants via nasal cannulas. Am J Dis Child. 1989;143(12):1458-60. Epub 1989/12/01. PubMed PMID: 2589278.
25. Benaron DA, Benitz WE. Maximizing the stability of oxygen delivered via nasal cannula. Arch Pediatr Adolesc Med. 1994;148(3):294-300. Epub 1994/03/01. PubMed PMID: 8130865.
26. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000;105(2):295-310. Epub 2000/02/02. PubMed PMID: 10654946.
27. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. Pediatr Pulmonol. 1996;21(1):48-51. Epub 1996/01/01. doi: 10.1002/(SICI)1099-0496(199601)21:1<48::AID-PPUL8>3.0.CO;2-M. PubMed PMID: 8776266.
28. Jackson JK, Ford SP, Meinert KA, Leick-Rude MK, Anderson B, Sheehan MB, et al. Standardizing nasal cannula oxygen administration in the neonatal intensive care unit. Pediatrics. 2006;118 Suppl 2:S187-96. Epub 2006/11/03. doi: 10.1542/peds.2006-0913Q. PubMed PMID: 17079622.
29. Bloch-Salisbury E, Indic P, Bednarek F, Paydarfar D. Stabilizing immature breathing patterns of preterm infants using stochastic mechanosensory stimulation. Journal of applied physiology. 2009;107(4):1017-27. Epub 2009/07/18. doi: 10.1152/japplphysiol.00058.2009. PubMed PMID: 19608934; PubMed Central PMCID: PMC2763836.
30. Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). J Pediatr. 2014;165(2):240-9 e4. Epub 2014/04/15. doi: 10.1016/j.jpeds.2014.02.054. PubMed PMID: 24725582; PubMed Central PMCID: PMC4111960.