

Feasibility and Impact of Volume Targeted Ventilation for preterm infants born < 32 weeks gestational age with need for invasive Positive Pressure Ventilation in the Delivery Room in reducing neonatal pulmonary morbidities

Phase I: Feasibility of Measuring Tidal Volume in the Delivery Room

Phase II: Feasibility of providing Volume Targeted Ventilation in the Delivery Room

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SPECIFIC AIMS AND HYPOTHESIS

Bronchopulmonary dysplasia (BPD) continues to be one of the most common long-term pulmonary complications associated with preterm birth. Despite significant decreases in preterm mortality, BPD rates in infants born ≤ 28 weeks gestational age have remained unchanged at approximately 40%^{i,ii,iii}. This probably is due to the multifactorial pathogenesis of BPD, with lung injury to the immature pulmonary tissue secondary to exposures including but not limited to antenatal/postnatal infection, free oxygen radical toxicity, and/or mechanical ventilation all leading to lung inflammation.

Delivery room (DR) practices of preterm infant during initial resuscitation can have a significant impact on occurrence and severity BPD. Current delivery room resuscitation for intubated preterm infants focuses on pressure limited ventilation (PLV), however, rapidly changing pulmonary compliance during the early newborn transition phase results in significant variability in the tidal volume provided to the infant, which in turn can lead to volutrauma, barotrauma and/or atelactetotrauma. A recent report suggested that pressure limited resuscitation devices routinely used in the delivery room are capable of tripling the intended Tidal Volume (TV)^x. No study thus far has evaluated the role of volume targeted ventilation (VTV) in the delivery room. Our short term goals are to assess the feasibility measuring TV in the DR, feasibility of providing VTV in DR, and to understand the pulmonary mechanics and physiology during VTV. Our long-term goal is to evaluate the efficacy of VTV versus PLV during DR resuscitation in reducing neonatal lung injury. In Phase I, we seek to demonstrate that measuring TV in the DR is feasible. In Phase II, we seek to demonstrate that providing volume targeted ventilation is feasible in the delivery room in infants born <32 weeks.

Specific Aims and Hypothesis, Phase I

Specific Aim #1: To assess feasibility of measuring TV in the DR for preterm infants <32 weeks with need for invasive positive pressure ventilation via endotracheal tube (ETT).

Hypothesis 1: We hypothesize that measurement of TV in intubated preterm infants <32 weeks in the DR is feasible.

Specific Aim #2: To assess variability in delivered TV in the DR with PLV for preterm infants <32 weeks with need for invasive positive pressure ventilation via ETT.

Hypothesis 2: We hypothesize that the TV generated via PLV in the immediate neonatal transition phase will be highly variable.

Specific Aims and Hypothesis, Phase II

Specific Aim #1: To assess feasibility of providing VTV, by quickly adjusting the peak inspiratory pressures (PiP) provided via the T-Piece resuscitator based on real time TV measurements.

Hypothesis 1: We hypothesize that real time PiP adjustments are feasible when utilizing a T-Piece resuscitator to provide VTV for goal TV of 4-6ml/kg.

Specific Aims #2: To compare the pulmonary mechanics and physiology during VTV, respiratory support requirements for infants receiving VTV versus PLV.

Hypothesis 2: We hypothesize that infants receiving VTV will require lower PiP, will have lower oxygen needs

Specific Aim #3: To assess complication rates and long term outcomes for infants receiving VTV versus PLV

Hypothesis 3: We hypothesize that VTV in the DR will have similar complication rates as compared to PLV with improved long term pulmonary morbidities..

Outcome and Implications: Successful pilot study will demonstrate that for preterm infants <32 weeks VTV in DR is feasible and safe; provides consistent measurable TV with lower PiP and decreased oxygen needs as compared to PLV. Data from this pilot study would then serve as a basis for a future RCT comparing the role of VTV with PLV in DR resuscitation and their impact pulmonary outcomes for preterm infants.

STATEMENT OF PURPOSE

Despite significant improvement in preterm infant survival, the incidence of bronchopulmonary dysplasia (BPD) in infants born ≤ 28 weeks gestational age (GA) has been relatively stable at $\sim 40\%$ ^{i,ii,iii}, with 10,000–15,000 new cases estimated annually^{iv}. Delivery room (DR) management of preterm infants during the initial resuscitation has a significant impact on future development of BPD. Current DR practice as recommended by the Neonatal Resuscitation Program (NRP), focuses on providing positive pressure ventilation (PPV) for intubated infants based on pressure limited ventilation (PLV). But with rapidly changing pulmonary compliance during the early newborn period, PLV may lead to under or over inflation of the lungs and induce significant volutrauma, barotrauma and/or atelectotrauma, all of which are associated in the pathogenesis of BPD. No studies have specifically reported tidal volume (TV) provided in the DR in intubated infants with current PLV practices. Similarly, no study has evaluated the safety and efficacy of volume targeted ventilation (VTV) in the DR and its impact on BPD.

With the proposed study, in Phase I, we aim to demonstrate that measuring TV in intubated infants receiving PPV via PLV is feasible. We also seek to demonstrate that with PLV, TV is highly variable in the first few hours of life, even with the same peak inspiratory pressures (PiP) due to rapidly changing pulmonary compliance. A successful Phase I will demonstrate that measuring TV is feasible in the DR, and with information on real time actual TV achieved during PPV, it is possible to target the TV for a goal TV by adjusting the PiP provided.

Phase II will be a pilot randomized control trial to demonstrate feasibility of VTV compared to PLV. We will also aim to understand the pulmonary mechanics and physiology during VTV. A successful Phase II will demonstrate VTV is feasible, is associated with stable TV, decreased peak inspiratory pressure and oxygen needs compared to PLV, and not associated with increased complications compared to PLV. It will thereby justify a larger randomized control trial with enough power to evaluate the efficacy of VTV in reducing BPD and other long term pulmonary morbidities for preterm infants.

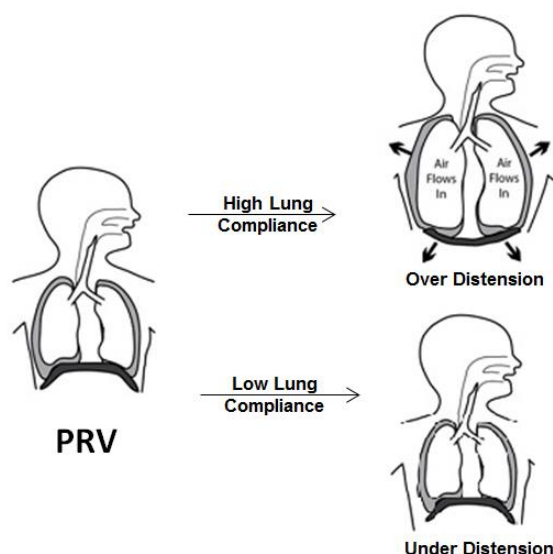
BACKGROUND

BPD continues to be one of the most common complications associated with preterm birth. A 2013 US study reported an increase in healthcare cost of \$31,565 associated with BPD, after controlling for birth weight, gestational age, and socio-demographic characteristics during the initial NICU hospitalization itself^{vi}. This economic burden starts from the initial NICU admission and persists through childhood and adulthood. A recent Spanish study published in 2013, reported that the healthcare related cost during the first 2 years of life of a preterm baby with BPD and no other major prematurity-related complications ranged between €45,049.81 and €118,760.43, in Spain, depending on birth weight and gestational age. If the baby required home oxygen therapy or developed pulmonary hypertension, this cost could further escalate to €181,742.43^{vii}. With 10,000–15,000 new cases of BPD annually in USA alone^{viii}, the economic impact of BPD is tremendous.

The pathogenesis of BPD is multifactorial, with lung injury from mechanical ventilation, oxygen toxicity, and antenatal or postnatal infections, all leading to lung inflammation which play a key role in the development of BPD. Delivery room (DR) management of preterm infants during the initial resuscitation is critical, and can have a significant impact on development of BPD. Studies have demonstrated that DR respiratory management with invasive respiratory support and higher oxygen content is associated with increased risk of death and/or BPD compared to non-invasive ventilation and lower oxygen resuscitation, respectively. Preterm infants stabilized on CPAP with prudent titration of supplemental oxygen in the delivery room to achieve targeted oxygen saturations have demonstrated improved rates of BPD^{ix}.

CURRENT STANDARD OF CARE PRACTICE

Current DR practice for intubated preterm infants focuses on pressure limited ventilation using either a self-inflating bag or a T-piece resuscitator where the provider regulates the inflation pressure and inflation time, but not the tidal volume.



As an infant transitions to extra uterine life, pulmonary compliance changes rapidly. Total pulmonary compliance is a composite of the lung and chest wall compliances. In preterm infants, the chest wall is composed primarily of cartilage rendering the chest wall highly compliant, and as a result, the neonatal lung is more prone to collapse. Preterm lungs additionally have reduced surfactant production which further decreases lung compliance. Upon initiation of positive pressure ventilation (PPV), the rapid fluid shift in the immediate newborn period can also result in swift changes in a newborn's pulmonary compliance. Provision of maternal antenatal steroids as well as surfactant replacement therapies can positively impact the preterm pulmonary outcomes. For these preterm infants, tidal volumes generated during PPV is directly proportional to the lung compliance as demonstrated by the formula:

$$C_{dyn} = \frac{V_T}{PIP - PEEP}, \text{ where, } V_T = \text{tidal volume};$$

PIP=peak inspiratory pressure; and PEEP=positive end-expiratory pressure.

Hence, with PLV the exact same pressure due to rapidly changing lung compliance may lead to under-inflation or over-inflation of the lungs.

Once admitted in the NICU, providing VTV to preterm infants is standard practice in our NICU, with inter-provider preference over volume versus pressure ventilation, with no true consensus. However, in the DR the practice continues to be utilizing PLV and with our proposed study we seek to provide physiologically more appropriate VTV to the preterm infants right from the birth in the DR.

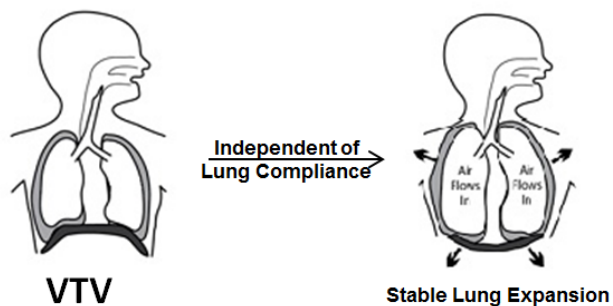
SIGNIFICANCE

With rapidly changing lung compliance in the immediate neonatal transition phase, PLV can lead to significant variability in the delivered TV. Recent reports suggests that pressure limited resuscitation devices routinely used in the delivery room are capable of tripling the intended TV while providing PPV in a newborn manikin^x. Large TV can lead to volutrauma, which is associated with adverse pulmonary outcomes. A study in preterm lambs showed as few as six large tidal volume breaths at birth can lead to acute lung injury and blunt the effect of subsequent surfactant treatment^{xi}. Ventilation with large breaths may cause gross overexpansion of regions that are forced open, leaving major parts of the lung blocked by fluid and unexpanded, and such regional over distension can be expected to cause epithelial and microvascular injury and pulmonary edema. The resultant pulmonary edema may make the lung more susceptible to further volutrauma during conventional mechanical ventilation^{xii}. Several animal studies have demonstrated that PPV with TV more than 8 mL/kg causes lung inflammation and lung injury^{xiii,xiv,xv,xvi}. Additionally, animal and human studies have demonstrated that excessive TV delivery during PPV in the delivery room causes brain inflammation and injury^{xvii,xviii,xix,xx}. Likewise, recent meta-analysis data demonstrate infants ventilated using volume targeted ventilation (VTV) modes reduce rates of death or BPD, pneumothoraces, hypocarbia, severe cranial ultrasound pathologies and reduce the duration of ventilation compared with infants ventilated using PLV modes. The risk of lung injury is in all likelihood related to the magnitude of the volutrauma at birth, and therefore ventilation immediately after birth needs to be very gentle^{xii}.

Without information about TV in the DR and rapidly changing lung compliance, PLV may lead to volutrauma. But no study has specifically evaluated the ability to measure TV provided in intubated infants in the DR or aimed at performing VTV in the DR while assessing its potential role in reducing lung injury.

INNOVATION

With recent advances in technology and ability to measure small TV at the endotracheal tube (ET) level with the help of flow sensors, TV can be measured accurately at the ET tube level and volume targeted ventilation (VTV)



becomes a possible alternative method of ventilating preterm infants. For our study, infants will have a flow sensor placed in series between the ETT and pressure generating device (T-piece resuscitator, self-inflating bag). The flow sensor will be connected to *Respironics NM3 monitor* (Philips Healthcare, Eindhoven, Netherlands) to measure the breath to breath TV. The flow sensor adds less than 1 mL of airway dead space volume (V_d) for neonatal sensors (ETT size of 2.5–4 mm). Phase 1 of our study will look into the feasibility of measuring TV in preterm infants. As some of the smallest VLBW infants may weight as less as 500gm,

goal TV range of 4-6ml/kg will be equal to 2ml-3ml per breath. No study has specifically looked into the ability of measuring such small tidal volume, and hence this feasibility study is of prime importance.

In Phase 2, by using the information of measured TV at the ETT level, the provider can quickly regulate the peak pressure delivered to the infant to achieve a goal TV of 4-6 ml/kg. The provider will be trained to increase or decrease the pressures, by following a strict protocol to ensure the TV remains at goal during neonatal resuscitation. As soon as the infant is stable, the infant will be transitioned to a ventilator with volume targeting capabilities. With stable lung expansion, infants receiving VTV will receive goal TV more consistently, will have reduced incidence of atelectotrauma, volutrauma and overall reduced lung injury with lesser long term pulmonary morbidities.

With the proposed study, in Phase I, we aim to demonstrate that measuring TV in the DR is feasible and is highly variable in the first few hours of life, even with the same peak inspiratory pressures due to rapidly changing pulmonary compliance. A successful Phase I will provide evidence that providing consistent VTV is possible in the DR by adjusting the PiP. In Phase II, we aim to obtain pilot data assessing the feasibility of VTV in the DR, and attempt to understand the pulmonary mechanics and physiology during VTV. A successful pilot study will demonstrate that VTV is feasible; is associated with consistent delivered TV; lower PiP and oxygen needs for the patients; thereby justifying a larger randomized control trial to evaluate the efficacy of VTV in reducing BPD and long term pulmonary morbidities.

HYPOTHESIS

PHASE I:

Primary Hypothesis: We hypothesize that measurement of TV in intubated preterm infants <32 weeks in the DR is feasible.

Secondary Hypothesis: We hypothesize that the TV generated via PLV in the immediate neonatal transition phase will be highly variable.

PHASE II:

Primary Hypothesis: We hypothesize that real time PiP adjustments are feasible when utilizing a T-Piece resuscitator to provide VTV for goal TV of 4-6ml/kg that can be seamlessly transitioned in the NICU.

Secondary Hypothesis:

- i. We hypothesize that infants receiving VTV will require lower PiP, will have lower oxygen needs with improved long term pulmonary morbidities
- ii. We hypothesize that VTV will have lower complication rates as compared to PLV.

SPECIFIC AIMS:

PHASE I:

Specific Aim #1: To assess feasibility of measuring TV in the DR for preterm infants <32 weeks with need for invasive positive pressure ventilation via endotracheal tube (ETT).

Objectives:

Date 10/15/2018

Protocol Version-I

- To assess the % infants with all equipment ready(including NM3 monitor and flow sensor) in DR to measure TV
- To assess the % infants where TV was measured within 60 seconds of ETT placement and positive pressure ventilation initiation.

Specific Aim #2: To assess variability in delivered TV in the DR with PLV for preterm infants <32 weeks with need for invasive positive pressure ventilation via ETT

Objectives:

- To assess the % infants with tidal within goal of 4-6ml/kg via routine PLV
- To assess the % infants with under or over ventilation using routine PLV
- To assess changes in TV with administration of surfactant with the same pressures

PHASE II:

Specific Aim #1: To assess feasibility of providing VTV, by quickly adjusting the peak inspiratory pressures (PiP) provided via the T-Piece resuscitator based on real time TV measurements.

Objectives:

- To assess the recruitment rates and successful enrollment into the study
- To assess the % of infants with measurable TV and successful adjustment of PiP to reach goal TV
- To assess the % of infants who fail VTV and need to be switched to conventional PLV

Specific Aims #2: To compare the pulmonary mechanics and physiology during VTV, respiratory support requirements

Objectives:

- To compare TV delivered during PLV versus VTV.
- To compare FiO2 requirement during PLV versus VTV
- Evaluate PiP, mean airway pressures (Paw), peak end expiratory pressures (PEEP) and oxygen requirement during the first 48 hours between the two study arms.
- Evaluate differences in blood gas results (pH, PCO2 levels).

Specific Aim #3: To assess complication rates and long term outcomes for infants receiving VTV versus PLV.

Objectives:

- To compare the total duration of neonatal resuscitation before reaching a stable state ready for transfer to NICU from the DR
- To record APGAR scores as a means to evaluate the ongoing resuscitation
- Compare oxygen requirements between VTV and PLV group during DR resuscitation
- To assess the incidence of complications including pneumothorax
- To evaluate for other unexpected adverse events that may be associated with VTV
- Evaluate longer term pulmonary morbidities: duration of invasive ventilation, BPD rates, and home oxygen requirements at discharge.

DESIGN AND PROCEDURE

EXPERIMENTAL DESIGN

Phase I: Phase I will be an observational, non-interventional study. All infants will receive routine resuscitation as recommended by the NRP. A flow sensor device connected to Respironics NM3 monitor (*Philips Healthcare, Eindhoven, Netherlands*), will be placed between the ETT and T-piece resuscitator to measure breath to breath tidal volume. Providers will be blinded from the actual TV measurements as in routine clinical scenario, and no intervention will be recommended or planned based on the TV measurements.

We will select a convenience sample of 10 patients. All preterm infants born < 32 weeks at Baystate Medical during the 1 year study period will be screened for possible inclusion.

Phase II: We will conduct a randomized control trial to assess feasibility of VTV in the delivery room compared to PLV in preterm infants.

SELECTION OF SUBJECTS

All preterm infants born < 32 weeks at Baystate Medical Center during the 1 year study period will be screened for possible inclusion. With annual delivery of approx. 4000 infants, of which 80-100 infant born < 32 weeks gestation, there will be sufficient patient population for the proposed pilot study.

Inclusion Criteria:

- Gestational age < 32 weeks of gestation
- Infant born at Baystate Medical Center
- Requiring intubation and positive pressure ventilation in the delivery room
- Parental Consent

Exclusion criteria:

- Maternal prolonged rupture of membrane > 2 weeks duration
- Known congenital or cardiac abnormalities or discovered in the immediate neonatal period.

Withdrawal/Termination Criteria:

- Withdrawal of parental consent

PHASE I: No specific withdrawal/termination criteria will be required as this is an observational study to assess feasibility of measuring tidal volume in the DR. Infant will continue to receive routine care as recommended by NRP, even if TV measurements are unsuccessful.

PHASE II: Control Arm: No specific withdrawal/termination criteria will be required, as these infant will continue to receive routine care per NRP recommendations without any study related intervention.

Intervention Arm: If TV cannot be measured or VTV cannot be provided within 60 seconds of initiating PPV via the ETT, the infant will be automatically switched to receiving routine care as recommended by the NRP.

INFORMED CONSENT PROCESS AND TIMING

Who: Parent.

When: “Deferred consent” is being requested after the birth of the child. The study process starts as soon as the baby is born and requires intubation as determined by the clinical team providing resuscitation. We will obtain a deferred consent from the parents only if the baby requires intubation in the delivery room and the TV measurements were obtained. We will approach the parents to use the data that was collected in the delivery room.

Rationale for deferred consent: *In an ideal situation, the consent should be obtained prior to study intervention. However, since the study intervention starts within few seconds to minutes of the baby's birth and it is not*

possible to determine which baby will need intubation in the delivery room, it would be unrealistic to have the opportunity to obtain informed consent we will aim for "deferred consent" process. As this study only present minimal risk to the infants and the device being used is an FDA approved device for use in neonates, a deferred consent is being requested for from the IRB.

How much time to decide: Since study related interventions has already occurred and we are asking parents to give consent for using this information as well as review of electronic medical records parents will have adequate time to make this decision free of any coercion to participate in the study.

Person authorized to obtaining consent: All investigators, program coordinator associated with the study.

SUBJECT FEES: None

REIMBURSEMENT/RENUMERATION FOR PARTICIPTION: None

RISK BENEFIT ASSESSMENT

Providing VTV to the VLBW infants is a standard of care practice upon admission to the NICU, with this study we seek to provide more physiologic VTV to the infant immediately after birth without any delay.

Phase I: No risk and no benefit directly to the patient, as this is the observational phase of the study. Information obtained from this phase study may potentially be beneficial by supporting the need for future studies in preterm infants with need for invasive respiratory support.

Phase II: Infants in intervention arm will receive the same routine care with additional information about the TV being delivered to the study infants. The provider's ability to adjust the PiP to provide goal TV may be potentially beneficial for the study infants, as in current DR practice the delivered tidal volume is unknown and infant may be receiving TV out of the set goal range. Infants in the control arm will not have any direct risk or benefit. The only concern would be adding less than 1ml of dead space with the flow sensor, which may or may not be of any clinical significance at all.

UNANTICIPATED PROBLEMS AND SERIOUS ADVERSE EVENT REPORTING

Unanticipated problems and serious adverse events to the subjects related to the study will be reported to the IRB within 48 hours of the occurrence.

RANDOMIZATION

Phase I: No randomization. All infants will receive pressure regulated breaths, 40-60 breaths/min, PiP of 20-24cm of H₂O as recommended by 2017 Neonatal Resuscitation Program (NRP) guidelines. Providers will be blinded from the measured TV during the resuscitation.

Phase II: All infants born <32 weeks will be randomized to one of the study group. Randomization will be via sealed envelope, opened in DR after the decision to intubate is made, with a 1:1 randomization ratio. To keep the gestational age in the two study arm relatively similar, as we are proposing only a small sample size for this current study, randomization will be stratified by gestation age group (Randomization subgroup I: <28 weeks and subgroup II: 28-32 weeks). Infants in both the arms will have a flow sensor at the ETT connected to Respiration NM3 monitor (Philips Healthcare, Eindhoven, Netherlands), to measure breath to breath TV.

INTERVENTION

Control Arm: Infant will receive pressure regulated breaths, 40-60 breaths/min, PiP of 20-24cm of H₂O as recommended by 2017 Neonatal Resuscitation Program (NRP) guidelines. Reading of the TV will be blinded from the providers as in routine clinical situations

Intervention Arm: Infants in the intervention arm will receive VTV following intubation. Peak inspiratory pressure (PiP) provided via T-piece resuscitator will be visible to the providers, and the provider can regulate the PiP to achieve the desired TV goal (4-6 ml/kg), at a rate of 40-60 breaths/min according to a predefined protocol

The infants will continue to receive respiratory support as assigned by the study arm for the first 48 hours of life, following which they will receive routine VTV and weaning as per standard of care NICU practice.

BLINDING

Phase I: Providers will be blinded from the measured TV during the resuscitation.

Phase II: Due to the providers being aware of ventilation process and the need for change in ventilator settings based on the infant's TV, blood gas, blinding the providers will not be possible. Acknowledging this, we will be blinding the outcome assessment. The individual collecting the data for the two groups and performing the physiologic BPD testing will be blinded on the infant's randomization status. Need for discharge home on oxygen will be assessed by a physician not associated with the study and strict guidelines will be followed for discharge home on oxygen. Provider performing long term outcome assessment will also be blinded from the infant randomization status during the study.

PRIMARY OUTCOME VARIABLE

Phase I: Successful measurement of tidal volume in within 60 seconds of intubation and initiation of PPV.

Phase II: Timing of initiation of VTV will be similar to PLV.

STUDY ENDPOINTS

The study patient will continue in the randomized arm for the first 48 hours of life with ongoing data collection for the first 48 hours after initial neonatal resuscitation. After the first 48 hours, infant will continue standard of care per the NICU providers, with continued data collection for longer term outcomes.

SAMPLE SIZE

Phase I: We will select a convenience sample of 10 successive patients for the initial phase of the study.

Phase II: We will enroll a total of 30 patients (15 per study group). The sample size was selected to insure sufficient number of patients to estimate variability and effect sizes^{xxi} and to estimate recruitment rates. For example, with 30 patients, the width of the 95% confidence will be about 55% as wide as the standard deviation. This estimate will help develop sample size estimates for future studies.

DATA COLLECTION AND STORAGE

Study data will be collected and managed using a secure, web-based, password protected RedCap (Research Electronic Data Capture) data base^{xxii}. Baseline demographic maternal and infant characteristics, TV, PiP, mean airway pressure, PEEP, FiO₂, resuscitation details, duration of invasive mechanical ventilation, duration of non-invasive respiratory support (non-invasive mechanical ventilation, continuous positive airway pressure), duration of oxygen treatment, home O₂ requirement, BPD incidence and severity along with pulmonary complications will be collected. Standard BPD definition of mild (oxygen use for 28 days), moderate (oxygen need at 36 weeks), or severe (ventilatory support at 36 weeks), along with physiologic BPD testing at 36 weeks will be used to define BPD. This data will also be used prospectively in a future randomized control trial if feasibility study is successful. The research team members and DSMB will have access to the full data set.

DATA ANALYSIS

As the study is designed as a pilot, no formal tests of hypotheses will be conducted^{xxiii}. In Phase I, our goal is to attain skill and competency with using the device, as well as to establish that our measures are reliable and valid. Descriptive statistics will be used to assess the feasibility of measuring TV in the DR. Feasible will be defined as being able to successfully measure the TV in 80% of the infants within 60 seconds of starting PPV via the endotracheal tube.

For Phase II of the pilot project, data analysis will be limited to point estimates (e.g., means and proportions). We will describe the feasibility of using VTV in the DR, and data analysis will be limited to estimating the point estimates (e.g., means and proportions) and variability of ventilatory measures in each group and overall. We will also estimate recruitment and attrition rates, as well as the duration of the consenting process.

We will use the pilot phase to begin identifying and assessing the frequency of adverse events for developing safety measures. Additionally, the pilot data will be used to estimate effect sizes and variability so that sample size and statistical power may be computed for a later randomized control trial.

Although this study will not be powered to evaluate differences in longer term pulmonary outcomes like BPD, we will still assess for possible trends in difference of BPD and other pulmonary outcomes between the two groups. Being a feasibility study, this study will not be powered to evaluate the safety and other long term outcomes between the two arms, but we will collect and analyze the safety data especially since we will be using the enrolled patient data for the future randomized control trial.

VULNERABLE POPULATION

This study involves studying newborn infants, who are considered vulnerable population. In phase I, the subjects involved in the study will have minimal risks as they will receive standard of care practices and we will only assess our ability to measure the TV in this population. In Phase II, the control arm has minimal risk as they will receive standard of care practices. The intervention arm may potentially have direct benefit as with the information about TV during resuscitation, we can target our PiP for goal TV, thereby minimizing volutrauma and/or atelectotrauma. Thus, overall this study poses none to minimal risk for the study subjects and may potentially benefit the infants in the intervention arm.

For the Phase II the study related interventions will be done only after a written informed parental consent has been obtained.

DATA AND SAFETY MONITORING

Safety data will be monitored closely for all enrolled subjects with special focus on infants randomized to the intervention arm in Phase II. Subjects in the intervention arm, based on the tidal volume generated, the maximum PiP will be limited at 30cm of H₂O, as it would be considered unconventional to require more PiP than 30cm of water in the immediate neonatal phase for longer than 60 seconds duration. If the tidal volume cannot be measured within 60 seconds, the patients will continue to receive conventional PLV during the time eliminating any potential harm to the patient. We will monitor for development of any pulmonary complication in the enrolled subjects including but not limited to pneumothorax, pneumo-mediastinum, and pulmonary interstitial emphysema.

- The DR staff including the attending neonatologists, advanced practitioners and respiratory therapists will be trained and will have ample time to feel comfortable about the flow sensor and the Respironics device prior to starting the study. Our staff currently uses a similar flow sensor device in the NICU and thus we do not anticipate any significant issues pertaining to training.

Subject stopping rules:

- Development of pneumothorax, pneumomediastinum
- PiP requirement >30 cm H₂O pressure for more than 60s
- Persistent low saturation or bradycardia with 60 seconds of optimum VTV

Individual responsible for stopping/modifying the protocol: **Dr. Robert Rothstein, MD**, Interim Division Chief along with the IRB will serve as the Safety Monitor for the study. Any SAEs will be reported to the IRB within 48 hours of occurrence.

POTENTIAL PITFALLS AND ALTERNATIVES

Inability to measure small tidal volume: As the *Respironics NM3 monitor* has never been tested to measure TVs in the range of 2-3ml/breath, we potentially run the risk of inability to measure the TV in this range in the extremely low birth weight infants (<500gm). We do plan to measure the TV in a standard test lung after acquisition of the device to ensure accuracy. Alternatively, we may have use the *Dräger Babylog VN500 ventilator* with a flow sensor device to measure TV in the DR. This will be more challenging as having a ventilator in the DR, but is possible to have one stand by, only to measure the TV from its circuit.

Leak from the ETT: Presence of a large leak may pose a significant problem in clinical situations as it makes accurate estimation of TV difficult. We will strictly adhere to the NRP guidelines for endotracheal tube sizes according the patients weight and gestational age and will evaluate both inspiratory and expiratory TV for the study. In situations with a large leak (>50%), we will use the expiratory TV as the marker for delivered TV.

Low intubation rates in the DR and low enrollment rate: With the increased usage of noninvasive respiratory support, the number of intubated infants in the DR might be lower than anticipated. In that situation, we are open to making this study a multicenter feasibility study with University of Massachusetts Medical School-Worcester as a potential partner. Additionally, for Phase I, we can also evaluate the feasibility of measuring TV in infants undergoing “INSURE” (intubation, surfactant and rapid extubation) for respiratory distress syndrome, as these infants also tend to be premature <32 weeks infants with rapidly changing pulmonary compliance after administration of surfactant therapy.

ANTICIPATED RESULTS AND IMPACT

Phase I: Tidal volume can be rapidly measured in more than 80% of intubated infants in the DR. TV is highly variable in the immediate newborn period, which can result in significant over or underdistension of the lungs, predisposing the infant to lung injury from volutrauma and/or atelectotrauma. A successful Phase I study will demonstrate the potential that a goal TV can be targeted during PPV by adjusting the PiP provided.

Phase II: We anticipate demonstrating that delivering VTV in DR is feasible for optimal lung recruitment; which when continued in the NICU may potentially reduce lung injury as well as long-term pulmonary complications including BPD. The study will provide evidence and pilot data to support the need for a larger, multi-center randomized control trial comparing VTV versus PLV during DR neonatal resuscitation. It will also provide evidence supporting the lung protective impact of VTV, and can potentially lead to significant change in practices from pressure limited to volume targeted respiratory support during neonatal resuscitation.

PUBLICATION PLANS

The results from the study will presented in various local, regional and national conferences, with the eventual goal of publishing the results in a peer review journal.

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