Study Title: Respiratory Mechanics Following Brain Injury: The role of inhaled nitric oxide

Principal Investigator: Michael Goodman

Sponsor: USAF 711th Human Performance Wing

1. **Length of time for research**
    a. 18 months patient enrollment and data collection
    b. 6 months data analysis and preparation of manuscript

2. **Research Location(s):** All subjects will be patients in the surgical or neurosurgical intensive care unit at the University of Cincinnati Medical Center. Study records will be maintained in the researchers' office in the MSB.

3. **Abstract/Brief Overview:**

    Intubation and mechanical ventilation are common treatments in the care of patients with traumatic brain injury (TBI). Intubation allows for airway control and facilitates removal of respiratory secretions. Mechanical ventilation allows control of arterial carbon dioxide to aid in control of intracranial pressure. Recent evidence suggests that lung protective ventilation (tidal volumes of 6 ml/kg of predicted body weight and moderate positive end expiratory pressure) improves outcomes following brain injury and reduces brain-lung cross talk.

    The treatment of respiratory failure in TBI must balance the need to improve lung function with the negative consequences of increased intrathoracic pressure on mean arterial pressure, intracranial pressure and venous return. Traditional treatment of increasing positive end expiratory (PEEP) and mean airway pressure then, represent competing interests. Methods for improving arterial oxygenation while avoiding negative hemodynamic effects are needed.

    The impact of head injury on respiratory mechanics has been studied in just a few clinical investigations. (1-3) Of note, the earliest of these noted that the ventilation perfusion (V/Q) matching following TBI was not the result of lung collapse or parenchymal lung disease but secondary to alterations in perfusion. There are three possibilities for this finding:

    1. redistribution in regional perfusion, which is partially mediated by the hypothalamus

    2. pulmonary microembolism, leading to increased dead space

    3. lung surfactant depletion due to excessive sympathetic stimulation and hyperventilation.

    The introduction of inhaled pulmonary vasodilators such as inhaled nitric oxide or aerosolized epoprostenol offer an opportunity to improve oxygenation in patients with TBI without increasing airway pressures in the face of V/Q inequalities.

    This study will evaluate the changes in respiratory mechanics following TBI and determine the effect of inhaled nitric oxide on gas exchange.

4. Purpose of Study:

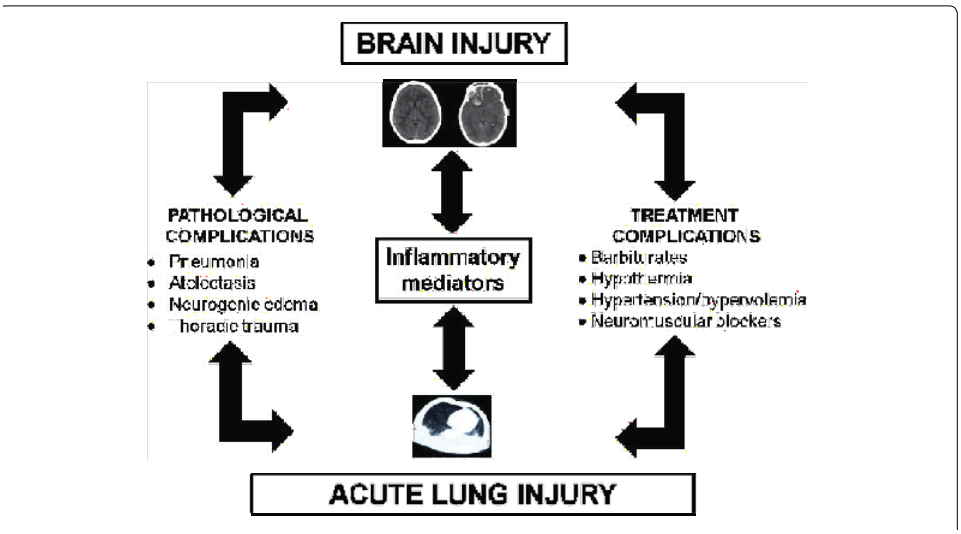
To determine the changes in respiratory mechanics in patients with traumatic brain injury (within 36 hours of admission and day 3 following admission.

To evaluate the effect of inhaled nitric oxide on gas exchange in patients with traumatic brain injury within 36 hours of admission.

Hypothesis: Inhaled nitric oxide improves oxygenation and reduces deadspace to tidal volume ratio following TBI.

5. Background:

Intubation and mechanical ventilation are common treatments in the care of patients with traumatic brain injury (TBI). Intubation allows for airway control and facilitates removal of respiratory secretions. Mechanical ventilation allows control of arterial carbon dioxide to aid in control of intracranial pressure. Recent evidence suggests that lung protective ventilation (tidal volumes of 6 ml/kg of predicted body weight and moderate positive end expiratory pressure) improves outcomes following brain injury and reduces brain-lung cross talk. Figure 1.



Respiratory failure following traumatic brain injury is a common complication resulting in hypoxemia and is associated with release of inflammatory mediators which may damage distal organs including the brain. The etiology of respiratory

failure following brain injury is multifactorial. Isolated head trauma is associated with neurogenic pulmonary edema and changes in ventilation perfusion matching. Concomitant trauma to the chest and pulmonary contusion may further worsen lung injury. It has been suggested that brain injury primes the lung to be a greater risk to a second hit (pneumonia, ventilator induced lung injury, lung contusion). Loss of consciousness can lead to aspiration of oral or gastric contents leading to pneumonia. Importantly, respiratory failure following TBI is implicated in 50% of deaths and prolonged ICU and hospital stay. (4,5)

The treatment of respiratory failure in TBI must balance the need to improve lung function with the negative consequences of increased intrathoracic pressure on mean arterial pressure, intracranial pressure and venous return. Traditional treatment of increasing PEEP and mean airway pressure then, represent competing interests. Methods for improving arterial oxygenation while avoiding negative hemodynamic effects are needed.

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In 1983, Cooper and Boswell demonstrated that hypoxemia in a series of 21 patients with head injury was related to a decrease in functional residual capacity and increased shunt. (2) In this study the addition of 10 cm H_2O PEEP reversed the fall in FRC and improved oxygenation. However, these patients were all paralyzed and nursed in the supine position. Paralysis and the supine position are known to decrease FRC even in normal subjects under anesthesia.

More recently, Koutsoukou et al evaluated 21 subjects with brain injury (intracranial hemorrhage and TBI) and no evidence of acute lung injury and found that PEEP of 10 cm H_2O prevented a deterioration in respiratory mechanics at five days. On day 1, PaO_2/FIO_2 was > 400 (FIO_2= 0.46) but both lung elastance and airways resistance were slightly elevated in both groups. These findings are not

unexpected in the presence of an endotracheal tube in a sedated subject lying in bed head up. These changes in respiratory mechanics worsened after day 5 and only elastance was spared in the group receiving 10 of PEEP. (3)

Mechanical ventilation following TBI is provided with the normal goals, reduce the work of breathing, provide adequate oxygenation, maintain normo- or hypocapnia and avoid lung injury. However, in an effort to improve brain tissue PaO_2 (TbO_2) mechanical ventilation in TBI may include increases in mean airway pressure and FIO_2 unrelated to the degree of lung dysfunction. Ventilatory support is always a balance of competing interests. Increases in airway pressure by increasing tidal volume, prolonging inspiratory time or increasing PEEP must be balanced against the risk of lung injury and hemodynamic interference. In TBI these must be furthered balanced against the impact on mean arterial pressure, cerebral perfusion pressure and venous return. (6)

Inhaled nitric oxide (INO) is a selective pulmonary vasodilator that at low doses (5-20 ppm) improves V/Q matching and at higher doses (80 ppm) reduces pulmonary artery pressures. Nitric oxide plays a role in a number of biologic processes and pathways that have been associated with improvements in brain function. (7,8) INO has been used in patients with TBI with successful increases in oxygenation in small case series. (10-11). These reports are not systematic applications of INO but rather rescue therapy in the face of ARDS.

The use of INO in ARDS has not proven to impact outcomes. (12-13) Several studies have shown improved gas exchange but no changes in morbidity or mortality. Despite these findings, INO is often used in ARDS to help improve gas exchange without increasing the risk of lung injury by increasing lung volumes or pressures.

This study will determine the etiology of lung dysfunction following TBI and describe the effect of INO on cardiorespiratory variables.

Inhaled nitric oxide (INOmax) is FDA approved and delivered via the INOmax DS_{IR} and FDA cleared delivery and monitoring device. The use of inhaled nitric oxide is limited to a maximum of 80 ppm. We will deliver 20 ppm, a dose that is widely prescribed.

6. **Study design:**

This study will determine the impact of inhaled nitric oxide on gas exchange and hemodynamics in a series of up to 43 patients with TBI over an 18 month period. The delivery of INO will be blinded. The study will also describe the changes in respiratory mechanics over a 3 day period.

All subjects ≥ 18 years of age, admitted to the University of Cincinnati Medical Center with traumatic head injury requiring mechanical ventilation within 24 hours of admission will be screened for enrollment.

Following informed consent, patients will have assessments of respiratory function accomplished using the existing monitors within the mechanical ventilator. The NM3 respiratory monitor and airway sensor will be placed for continuous recording of data. Within 36 hours of admission, the following measurements will be made by the study staff:

1. Static and dynamic lung compliance using tidal volume and airway pressures (CLstatic = Pplat -PEEP/VT) CLdynamic= Pplat - PEEP/VT). These measurements are made non-invasively using the integral monitoring of the mechanical ventilator.
2. Airway resistance using airway pressures and flow (Raw = Pplat - PEEP/Mid Expiratory flow). These measurements are made non-invasively using the integral monitoring of the mechanical ventilator.
3. Dead space to tidal volume ratio (Vd/Vt) will be calculated using the Enghoff modification of the Bohr equation: $Vd/Vt = PaCO_2 - PeCO_2/PaCO_2$, where Vd is the dead space volume and Vt is the tidal volume; $PaCO_2$ is the partial pressure of carbon dioxide in the arterial blood, and $PeCO_2$ is the mixed expired partial pressure of carbon dioxide in the expired (exhaled) air. In the absence of arterial blood gases we will calculate $PaCO_2$ from determination of alveolar concentrations ($PACO_2$) in expired gas.
4. Functional residual capacity (FRC) will be measured by the automated system within the GE Carestation ventilator, which uses a step change in FIO_2 to measure FRC through nitrogen washout while monitoring oxygen consumption and carbon dioxide production. These measurements are made non-invasively using the integral monitoring of the mechanical ventilator.
5. Positive end expiratory pressure (PEEP) will be titrated from baseline PEEP as set at time of enrollment to-15 cm H_20 (in 5-cm H_2O increments) while measuring all the variables listed in #1-4 above. This method will determine the best PEEP and determine recruitability of the lung. FRC will be measured at three levels of PEEP from baseline to a maximum of 15 cm H_2O. This is an automated measurement requiring approaximately 15 minutes to complete. If the patient develops hypotension (systolic pressure < 90 mm Hg or mean arterial pressure < 60 mm Hg) participation in the PEEP trial will be terminated.
6. Following these initial measurements, patients will be randomized to receive either a placebo (nitrogen and oxygen) or inhaled NO at 20 ppm for 2 hours ± 30 minutes. After receiving the placebo or inhaled NO, the measurements in #1-4 will be reassessed (no change in PEEP will be made during this time unless required for clinical purposes).
7. If the patient remains on the ventilator at day 3 (72 hours after admission), 1-6 above will be repeated.

Subjects will receive placebo or drug for no more than 5 hours total.

If the patient responds to NO with a brisk increase in SpO2 or PaO2 – sudden withdrawal of NO can result in a fall in oxygenation (rebound pulmonary hypertension). This is uncommon in the absence of pulmonary hypertension. Prevention of rebound pulmonary hypertension is accomplished by increasing FIO2 by 10-20% prior to discontinuation of NO, followed by a return to baseline FIO2 over 30 mins.

If ICP goes up by >20% NO will be discontinued.

7. Research data collection/study procedures:

The patient baseline demographics including injury mechanism, severity and distribution, Glasgow coma scale score, age, gender, any witnessed aspiration, and lung mechanics measurements listed above will be collected to data sheets and then entered into a RedCap database. We will also record ventilator settings, lung compliance, airways resistance, dead space to tidal volume ratio, functional residual capacity, blood gases and duration of total mechanical ventilation, days in the ICU, hospital days and survival will be collected from the medical record and also entered into the RedCap database. See sequence of events for study measures.

8. Specimen collection:

The following blood samples will be taken:

At baseline up to 3.5 ml will be taken. 1.5 ml for arterial blood gas testing (tests include: arterial pH, $PaCO_2$, PaO_2, SaO_2 and $HCO_{3)}$) and 2 ml for measurement of inflammatory mediators specific to the lung.

After 90 to 120 minutes of nitric oxide/placebo delivery, less than 1.5 ml will be taken for arterial blood gas testing.

At the end of the study, up to 3.5 ml will be taken. 1.5 ml for arterial blood gas and 2 ml for measurement of inflammatory mediators specific to the lung.

The blood will be taken from indwelling lines when possible. If we are unable to obtain any of the blood samples, the subject will remain in the study and all other data will continue to be collected

9. **Potential Benefits:**

The detailed measurement of respiratory mechanics will be provided to the clinical team. This information which is not routinely measured can be used to optimize ventilator support beyond traditional monitoring. The determination of FRC and recruitability of the lung may assist the clinical team in identifying the best PEEP for each individual patient.

If the patient has a significant increase in PaO_2 associated with INO/placebo delivery, the clinical team can use that information to implement INO therapy as part of clinical care. It is unlikely that placebo will increase oxygenation appreciably. We will not unblind the study, the clinical team will have to make this decision based on a supposition of INO delivery.

Understanding the changes in respiratory function following TBI and the response to INO may improve treatment regimens for future patients.

10. Potential Risks, Discomforts, and inconveniences:

Level of risk: Greater than minimal risk.

The measurements to be made utilize non-invasive measures of lung volumes, flows, and pressures to determine mechanics.

Arterial puncture/venipuncture may cause pain/discomfort, bruising, fainting, and infection from phlebotomy sites.

Hypotension in severe pulmonary hypertension and left ventricular failure (very uncommon).

Methemoglobinemia has only been reported at 80ppm.

The stepwise increase in PEEP to determine changes in FRC will be limited to a maximum of 15 cm H_2O. PEEP can decrease venous return and cause transient hypotension. The risk of hemodynamic compromise at these low pressures is small. All subjects will have blood pressure and heart rate continuously monitored (as is standard of care) throughout the measurements.

Research personnel will remain at the bedside throughout the measurements of respiratory mechanics which will require approximately 30 minutes to complete.

11. Data Safety monitoring plan and/or DSMB:

Dr. Jason Schrager will act as medical monitor for the study. He will review subjects' research data and adverse events to ensure patient safety. The medical

monitor will have the power to temporarily or permanently halt enrollment if it is deemed that patient safety is compromised.

12. Data Analysis:

Descriptive statistics will be employed to summarize relevant patient demographic factors as well as on baseline measurement of clinical variables. As a check on the success of randomization, these variables will be compared between groups using t-tests or chi-square tests, as appropriate.

The primary endpoint for this study is a change in PaO_2:FiO2 ratio of 20 percent or greater between baseline and Day 3. The proportions of patients achieving success according to this criterion will be compared between groups using a two-sided z-test with pooled variance

Group sample sizes of 19 in group one and 19 in group two achieve 82% power to detect a difference between the group proportions of 0.40. The proportion in group one (the treatment group) is assumed to be 0.10 under the null hypothesis and 0.50 under the alternative hypothesis. The proportion in group two (the control group) is 0.10. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05. The significance level actually achieved by this design is 0.0361.

Respiratory mechanics will be presented as descriptive (Mean, SD, range). Up to 43 subjects may be enrolled, in order to obtain the required 38 evaluable subjects. Patients will be removed from the study and its analysis if extubated by the clinical treatment team during the 72 hour NO protocol.

13. Data storage and confidentiality (include sample storage if applicable)

We will ensure that paper forms are stored securely under lock and key when not in the direct custody of an investigator. Forms may have direct identifiers for the purposes of linking data from different medical records. Electronic data will not be entered with direct identifiers. A subject number will be used to link back to the identifier. The key linking identifier to subject number will not be stored with the electronic data. Electronic data will be stored in a password protected Redcap database. Analytical datasets will be stored on secure servers that also limit access to the investigator team. Should results of the study be published or reported, individual names or other identifying information will not be used. One year after the study and publication are complete the data will be destroyed.

14. Study Population

All subjects ≥ 18 and ≤ 75 years of age, admitted to the University of Cincinnati Medical Center with traumatic head injury requiring mechanical ventilation within 24 hours of admission will be screened for enrollment. Inclusion criteria will include:

1. TBI with head CT findings of injury by penetrating or blunt mechanism
2. Requiring mechanical ventilation within 24 hours of admission
3. Negative pregnancy test

Exclusion criteria will include:

1. Brain death
2. Expected survival < 48 hours
3. Pneumothorax causing chest tube to be placed
4. Elevated inspired oxygen concentration (FiO_2 > 0.65) on assessment
5. Hemodynamic instability (systolic BP < 100 mmHg, cardiac arrhythmias)
6. Uncontrolled ICP (>20 mmHg) necessitating bolus hypertonic saline therapy
7. Unilateral or bilateral pupil dilation and no reactive pupil
8. Spinal cord injury with hypotension
9. Severe ARDS (PaO_2/FIO_2 < 100)
10. Flail sternum or unilateral flail chest wall segment (2 places on ≥ 3 ribs)
11. Pulmonary contusion or lobar infiltrate visible on admission chest xray
12. Chronic lung disease with PCO_2 > 60mmHg and HCO_3^- > 32mmol/L
13. ICP >20mmHg longer than 30 minutes despite hypertonic saline or mannitol therapy
14. Known heart failure (heart failure defined as EF<20%)
15. CVP > 20 mm Hg with associated systolic blood pressure < 100mmHg

15. Consenting process and plan

Study personnel will screen patients for inclusion and exclusion.

Due to the study population, all patients will be cognitively impaired due to their injuries, therefore surrogate consent will be obtained. Prior to approaching the patient's LAR/nok we will contact the patient's admitting physician and the ICU attending to assure their assent for patient enrollment.

The LAR/next of kin is identified using the social worker's note and contact information at the patient's bedside maintained by the nursing staff. Once the

LAR/next of kin is identified, the investigator and/or the study coordinator arranges to meet the LAR/next of kin in a private waiting room. The study staff allows the LAR/next of kin to decide if additional family members, friends, or advisors will be present. We frequently speak to the LAR/next of kin with a clergy member present or a family friend who has a medical background.

The informed consent, including the Health Insurance Portability and Accountability Act (HIPAA) authorization language approved by the University of Cincinnati and University of Cincinnati Medical Center's legal teams, is presented and reviewed to the LAR/nok and any questions are answered.

The study is time sensitive but LAR/nok will be allowed to review the consent document for 12 hours. A phone number is provided for the LAR/nok to call with additional questions. Subjects who cannot be enrolled during the first 36 hours after admission to UCMC will be considered screen failures.

Once subjects are deemed to be able to provide informed consent, the researchers will take them through the consenting process.

16. Compensation:

None.

17. Subject costs:

None**.**

18. Literature cited

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