Brooke Army Medical Center
Institutional Review Board

HUMAN SUBJECTS RESEARCH
PROTOCOL APPLICATION – Part B

1. PROTOCOL TITLE: Analysis of Preoxygenation Combining Nasal Cannula with Noninvasive Positive Pressure Ventilation

2. ABSTRACT: Noninvasive positive pressure ventilation with the addition of a nasal cannula is a useful technique to pre-oxygenate and provide apneic oxygenation in hypoxic patients undergoing emergency airway management. This study aims to evaluate preoxygenation by quantifying end-tidal oxygen (etO2) concentration resulting from nasal cannula placement underneath a noninvasive positive pressure ventilation (NIPPV) mask. This is a prospective randomized cross over study of healthy volunteers undergoing continuous positive airway pressure ventilation via a noninvasive ventilation (NIV) mask with and without the addition of nasal cannulas. End-tidal oxygen concentration will be measured by an oxygen sensor following three minutes of NIPPV with and without the addition of a nasal cannula, with each subject serving as his or her own control.

3. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTION*:* The objective is to compare end-tidal oxygen concentration among healthy volunteers undergoing NIPPV with nasal cannulas versus without nasal cannulas. We hypothesize that the use of nasal cannulas during NIPPV will not result in a significant decrease (a clinically significant difference of 5%) in end-tidal oxygen percent compared to no use of nasal cannulas.

4. MILITARY RELEVANCE: Effective means to improve oxygen saturations is critical during emergency airway management in any setting, including the deployed and austere environments frequently encountered by military medical providers.

5. BACKGROUND AND SIGNIFICANCE.
Multiple pre-oxygenation techniques are utilized to provide safe intubation conditions during emergency airway management. In a subset of patients, standard techniques such as tidal volume breathing of high FiO_2 source for three minutes or eight vital capacity breaths will fail to adequately pre-oxygenate and lead to early desaturation. Alternative pre-oxygenation techniques utilizing NIPPV or nasal cannula during the apneic period have been shown to benefit patients at risk for critical desaturation during intubation.[1, 2, 3]

Patients that fail to achieve oxygen saturations greater than 93% after tidal volume breathing from a high FiO_2 source are at risk for critical desaturation during an intubation attempt[4] and are likely exhibiting shunt physiology.[5] Shunt physiology refers to the process wherein blood perfusing fluid filled or collapsed alveoli is not adequately oxygenated, and then mixes with oxygenated blood from the remainder of functioning alveoli, contributing to hypoxia. Augmentation of mean airway pressure by NIPPV can improve shunt physiology and increase oxygen saturation prior to intubation attempts. In a study by Baillard et al, hypoxic ICU patients pre-oxygenated with pressure support ventilation via facemask had higher mean oxygen saturation prior to intubation when compared to patients undergoing pre-oxygenation with non-rebreather (98% vs 93%). Additionally, patients pre-oxygenated via non-rebreather desaturated to much lower levels during the intubation compared to the noninvasive group (81% vs 93%).[1]

However, many NIPPV machines (mainly BiPAP machines) do not supply continuous flow of oxygen during the apneic period. Oxygen administration via nasal cannula during the apneic period can increase the time to desaturation. In a study comparing apneic oxygenation with nasal cannula at 5L/min to patients on room air by Ramachandran et al, patients placed on nasal cannula had significantly prolonged time of saturations above 95% (5.29 vs 3.49 min). Also, a greater number of patients with nasal cannula during the apneic period had saturations above 95% at the end of six minutes (8 vs 1).[3]

The combination of both NIPPV and nasal cannula for pre-oxygenation and apneic oxygenation may be helpful to improve oxygen saturations during emergency airway management. Patients with shunt physiology requiring NIPPV to improve oxygen saturations prior to intubation will likely benefit from continuation of positive pressure during the apneic period.[5] The addition of nasal cannula provides apneic oxygenation during the period between sedative and paralytic administration and initiation of laryngoscopy. Preplacement of the nasal cannula under the NIPPV mask prior to medication administration also allows immediate transition to laryngoscopy with continued apneic oxygenation. We have previously shown that the nasal cannula does not significantly alter NIPPV mask seal (manuscript in review). Prior studies have evaluated the use of nasal cannula under a Bag-valve mask and anesthesia circuit with mask, showing a small but not statistically significant decrease in end-tidal oxygen concentration. [6,7] In addition, this study differs from previous studies in that other studies have used 5 LPM[7] and 10 LPM[6] through the NC instead of 15 LPM which is the flow rate recommended by a commonly cited review article on pre-oxygenation for emergency airway management. [5] This study aims to evaluate the effects on end-tidal oxygen concentration utilizing NIPPV commonly employed in the emergency department with the addition of a nasal cannula.

6. **RESEARCH DESIGN:** This is a randomized cross over study. A convenience sample of staff and resident physicians and physician assistants from the San Antonio Military Medical Center (SAMMC) Department of Emergency Medicine will be used to assess end-tidal oxygen saturations following a period of NIPPV using CPAP with and without nasal cannula. Volunteers will be solicited via weekly Emergency Medicine Grand Rounds and staff meetings at SAMMC. Subjects will undergo permuted randomization by random number generator in blocks of 4 to randomize the order of intervention: NIPPV mask alone or NIPPV mask with nasal cannula at 15L/min of oxygen. An emergency medicine trained physician will place equipment and operate the ventilator. After placement of the NIPPV mask and prior to each study intervention period, appropriate adjustments to enhance mask seal will be made as would happen in a therapeutic setting and subsequently the volunteer will undergo three minutes of continuous NIPPV. End-tidal oxygen concentrations will be measured at the end of the three minute ventilation period using an oxygen sensor.

7. RESEARCH PLAN

7.1 Selection of Subjects

7.1.1. Subject Population. The accessible study population will be a convenience sample of healthy adult volunteers. Each subject will serve as their own control.

7.1.2. Source of Research Material.

Source of Research Material	Clinical Purposes(Y/N)	Research Purposes (Y/N)
End-tidal oxygen concentration	N	Y

7.1.3. Inclusion and Exclusion Criteria.
Inclusion criteria include any healthy adult volunteer 18 years or older.

Exclusion criteria include previous inability to tolerate noninvasive positive pressure ventilation with addition of a nasal cannula. Known underlying cardiac or pulmonary disease. Active respiratory infections.

7.1.4. Description of the Recruitment and Prescreening Process. Subjects will be recruited volunteers and be solicited via Emergency Medicine Grand Rounds and staff meetings at SAMMC. Announcement of the study as well as dates and times of study session to obtain further information for participation will be made in a large group setting to avoid potential peer influence. Interested staff will be advised to attend a study session to learn

more about taking part. Potential subjects are able to opt out at any time, prior to or after arriving to receive further information about the study.

7.1.5. Subject Screening Procedures. Screening will involve a verbal willingness to participate in this study. Subjects will be asked if they have been unable to tolerate CPAP and nasal cannula previously, have known cardiac or pulmonary disease or if they have an active respiratory infection. No medical history will be documented. No physical examination will be required to determine eligibility or suitability.

7.1.6. Consent Process. The PI and AIs will be responsible for obtaining informed consent, explaining the study, and answering questions. Subject volunteers will be informed of the study purpose and plan immediately prior to a study session. They will be given an opportunity to have all of their questions answered by the research team. Written informed consent will be obtained individually prior to each scheduled study session in a private area.

7.1.7. Compensation for participation. Subjects will not be compensated for participation.

7.2 Drugs, Dietary Supplements, Biologics, or Devices.

7.2.1 Drug, biologic, dietary supplements- N/A

7.2.2 Devices
Respironics V60 Non-invasive ventilator.

- Safety: standard supply noninvasive ventilator
- Dose: CPAP 5cmH_2O
- Duration: 3 minutes for two intervention periods

Respironics AF521, EE with CapStrap headgear. Oro-nasal NIV mask

- Safety: standard supply noninvasive mask for use with Respironics V60
- Use with Non-invasive ventilator

Fisher&Paykel RT219 Noninvasive Adult Circuit

- Safety: standard supply circuit for use with Respironics V60
- Use with Non-invasive ventilator

Carefusion AirLife Standard Nasal Cannula, Ref#001325

- Safety: standard supply nasal cannula
- Flow Rate: 15L/min

Maxtex MaxO_2 oxygen analyzer

- Safety: standard supply portable oxygen analyzer

Maxtec Max-250E oxygen sensor

- Safety: standard oxygen sensor
- Use with Maxtec MaxO_2 oxygen analyzer

7.3. Study Procedures/Research Interventions. After obtaining consent, subjects will undergo randomization to order of intervention: NIPPV with (intervention) and without addition of nasal cannula at 15L/min of oxygen (control). Before the initial intervention, subjects will exhale through an oxygen sensor to determine baseline end-tidal oxygen concentration. For NIPPV without nasal cannula, subjects will have a CPAP mask placed and fitted appropriately. The NIV will be set to CPAP mode at 10cm H2O. During NIV with nasal cannula, subjects

will first be fitted with a standard adult nasal cannula at 15L/min flow of oxygen and then fitted for a NIV mask in the same fashion as NIV without nasal cannula. For each trial, subjects will undergo three minutes of spontaneous restful tidal volume ventilation while on CPAP via NIV mask. At the end of three minutes, subjects will remove the NIV mask and immediately exhale through an oxygen sensor, avoiding inhaling room air. After completion of the first arm, subjects will be given at least five minutes of breathing room air before undergoing the second phase of testing. Before beginning the second phase, subjects will exhale through the oxygen sensor to ensure return to baseline end-tidal oxygen concentration. If baseline has not been met, subjects will be allowed to breathe room air until end-tidal oxygen concentrations return to baseline levels. Subjects will then repeat the procedure of three minutes of spontaneous restful tidal volume ventilation while on CPAP via NIV mask, followed by an immediate exhalation through the oxygen sensors for measurement of end-tidal oxygen concentration.

7.3.1 Collection of Human Biological Specimens. N/A

7.3.1.1 Laboratory evaluations and special precautions. N/A

7.3.1.2 Specimen storage. N/A

7.3.2 Data Collection. The order of intervention will be annotated on the data collection form. Subjects will document their age, gender, height and weight. End-tidal oxygen concentrations will be collected before intervention to determine baseline, at the end of each intervention, and prior to beginning the second intervention to ensure return to baseline. All data forms will be kept in a locked drawer within the locked office of the PI. All data forms will be double entered into a secure Excel database.

7.3.3. Human Biological Specimens/Tissue/Data Banking. N/A

7.4 Statistical Consideration

7.4.1 Sample Size Estimation. A clinically significant difference of 5% in etO2 was chosen to approximate an additional 30 seconds of safe apnea time ([5% etO2 x 2,500mL functional residual capacity] / 250mL/min oxygen consumption in 80kg man).[6,8] 34 subjects will be required to identify a difference of 5% etO2, with an alpha of .05, beta .1, and a standard deviation of 7. 10% are anticipated to withdraw. A goal of 38 subjects will be enrolled.

Estimate Required Sample Size	34
Estimate Participant Drop Out / Withdrawal	4
Total Enrollment Requirement	38

Enrollment at Each Site	
BAMC	38

7.4.2 Primary (i.e., primary outcome variables) and secondary endpoints. The primary outcome variable is end-tidal oxygen concentration measured at the end of each intervention. The measured end-tidal oxygen approximates the alveolar concentration and is a common measure of preoxygenation.[8] End-tidal oxygen concentration of 90% is achievable on an anesthetic circuit with a tight-fitting mask.[9]

Secondary outcomes: No secondary outcome will be measured.

7.4.3 Data analysis. A two-tailed student's T-test for paired samples will be used to analyze the data. Patients will be randomized to which intervention that is performed first to limit any bias by order of intervention. Each subject will serve as their own control.

7.7 Confidentiality. Data collection forms will be kept in a locked drawer in the locked office of the PI. Study data will be double-entered into spread sheet format for data analysis. No personally identifying information will be obtained on the data collection forms or data analysis spread sheet. Data collection forms will be kept until the time of study publication. Data analysis spread sheets will be stored on a personal BAMC network drive.

7.7.1 Certificate of Confidentiality. N/A

8.0 RISKS/BENEFITS ASSESSMENT

8.1 Risks. Subjects will be exposed to no greater than minimal risk. Risks include temporary local skin irritation due to noninvasive mask contact. Proper mask fit will be assessed by an emergency medicine physician. Transient eye irritation or sinus congestion will be minimized by ensuring appropriate mask fit. Additionally, mask placement will not exceed three minutes per intervention. Gastric distention will be minimized by using low airway pressures of 10cm H2O, well below the 20cm H2O threshold of the lower esophageal sphincter.[10] Claustrophobia or anxiety may occur with mask placement and increased airway pressure. Subjects will be allowed to remove the mask at any time during the study and withdrawal from the study. All subjects will be monitored by a trained respiratory therapist or emergency medicine physician.

8.1.2 Potential Benefits. There are no anticipated benefits for the study subjects. However, this study holds a potential benefit to patients who present needing emergent airway management by investigating ways to best pre-oxygenate subjects. By doing so, the potential exists to help minimize the complications associated with crash airways, namely, hypoxia.

9. ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND DEVIATIONS

9.1 The study protocol involves no more than minimal risk to subjects. The only adverse effects from the NIPPV that are expected are mild skin, mucosal, or nasal irritation from the CPAP or anxiety or claustrophobia from the NIPPV mask. If study subjects experience any of these adverse effects they will be allowed to immediately terminate the study protocol themselves or with the assistance of a respiratory therapist or emergency physician who will be available at all times during the study protocol.

9.2 Reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events and Deaths to the Office of the IRB, BAMC.

All unanticipated problems involving risk to subjects or others, serious adverse events, and all subject deaths related to the study will be reported within 48 hours of the research team's knowledge of the event by phone (210-916-0606), by e-mail (BAMC_IRB_AE@amedd.army.mil), by facsimile (210-916-1650) or via letter addressed to Human Protections Administrator, Office of the Institutional Review Board, Brooke Army Medical Center, Attn: MCHE-CI,3698 Chambers Pass, Fort Sam Houston, TX 78234-6315. A complete written report will follow the initial notification within 10 working days.

9.3 Research Monitor. – N/A- Study involves no more than minimal risk to study subjects.

10.0 WITHDRAWAL FROM STUDY PARTICIPATION. Subjects are able to end participation at any time by requesting removal of the NIV on mask or personally removing the device. There are no consequences from withdrawal.

11.0 USAMRMC Volunteer Registry Database. N/A

12.0 REFERENCES.

1. Baillard C, Fosse J. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med*. 2006;174:171-177

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3. Ramachandran SK, Cosnowski A. Apneic oxygenation during prolonged laryngoscopy in obese patients: a randomized, controlled trial of nasal oxygen administration. *J Clin Anesth*; 2010;2010:164-168.

4. Bodily, JB et al. Incidence and duration of continuously measured oxygen desaturation during emergency department intubation. Ann Emerg Med. 2016 Mar;67(3):389-95.

5. Weingart S, Levitan R. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med.* 2012;59:165-175.

6. Hayes-Bradley, C., et al., Efficacy of Nasal Cannula Oxygen as a Preoxygenation Adjunct in Emergency Airway Management. *Ann Emerg Med*, 2015.

7. Groombridge, C., et al., Assessment of Common Preoxygenation Strategies Outside of the Operating Room Environment. *Acad Emerg Med*, 2016. 23(3): p. 342-6.

8. Tanoubi I, Drolet P, Donati F. Optimizing preoxygenation in adults. *Can J Anesth*. 2009;56:449-466.

9. Bouroche G, Bourgain JL. Preoxygenation and general anesthesia: a review. *Minerva Anestesiol*. 2015;81:910-920.

10. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. *Br J Anaesth.* 1987;59:315–8.

13.0 TIME REQUIRED TO COMPLETE THE RESEARCH (including data analysis). Ten months will be required to enroll and complete data collection on all subjects. Two months will be required for data analysis.

14.0 STUDY CLOSURE PROCEDURES. The study will be closed after enrollment of the required number of subjects and analysis of the data. Submission of a protocol closure report will then occur. Data collection forms and information sheets will be maintained until publication of the data; ICD will be maintained within locked office in a locked box for a period of no more than 3 years.