Real Time Assessment of Pre-oxygenation Utilizing End-tidal Oxygen Measurements versus Single Breath End-Tidal Oxygen Measurements in Healthy Volunteers

Short Title: Pre-oxygenation with Real Time End-tidal Oxygen Measurements versus Single Breath Measurements

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Sponsors: None

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1. External (non-Emory) Collaborators: Not applicable

2. Precis/Abstract: A brief (usually 400 words or fewer) description of the study objectives, population, design, and outcome measures

Patients in the Emergency Department (ED) undergoing Rapid Sequence Intubation (RSI) are at risk for serious morbidity and mortality. In order to provide oxygen during the apneic period, it is common practice to provide pre-oxygenation prior to the start of the procedure with high flows of oxygen. Different methods of pre-oxygenation have been studied by taking a single breath end-tidal oxygen (EtO2) measurement with higher levels indicating more complete pre-oxygenation. However, there has not been any research examining methods of determining the quality of pre-oxygenation in real time.

This study examines the performance of a nasal cannula EtO2 measurement as compared to the gold standard of single breath end-tidal oxygen measurements in healthy volunteers. Study subjects will be placed on either a NRBM at different flow rates (15 LPM, 35 LPM, or Flush rate at 55 LPM) or a non-invasive ventilator facemask at various fractions of inspired oxygen levels (40%, 70% and 100%) for separate trials of 3 minutes at each flow rate or FiO2. At the end of each intervention, study subjects will perform a single breath end-tidal oxygen measurement by exhaling fully into a tube attached to an EtO2 sensor. In addition, a fourth trial arm will be done for both the NRBM and the NIV subjects that will correlate maximal readings from the real time EtO2 nasal cannula at the moment those maximal readings are obtained. The primary outcome will be the degree of correlation between real time EtO2 measurements (at the end of the three minute trial) and a single breath end-tidal oxygen measurement as measured by the k correlation coefficient, as measured for each trial. The secondary outcome will be the correlation of EtO2 between the nasal cannula sensor and the single breath sensor once stabilized at maximal readings.

3. Introduction and Background:

Background: Prior to ED RSI, it is necessary to provide patients with pre-oxygenation to displace nitrogen from the alveoli and replace it with oxygen. This allows the patient to maintain their arterial oxygen saturation during the apneic period of RSI. Patients who experience hypoxia during RSI are at higher risk for serious morbidity and mortality.[1] Techniques commonly employed to pre-oxygenate Emergency Department (ED) patients undergoing RSI include high flow oxygen via a non-rebreather mask (NRBM), a self-inflating bag-valve mask (BVM), or non-invasive ventilation (NIV). However, there are currently no studies that explore how to assess the quality of a patient's pre-oxygenation in real time prior to intubation.

Several recent studies that have assessed the use of single breath end-tidal oxygen to assess the effectiveness of various oxygenation strategies.[2-4] Typically, healthy volunteers are placed on 2 to 3 minutes of a certain pre-oxygenation strategy followed by exhalation of a single

breath into an end-tidal oxygen sensor. Higher end-tidal oxygen measurements are used as a marker for pre-oxygenation with higher percentages indicating more complete pre-oxygenation.

A goal EtO2 reading of 90% is typically used to indicate maximal pre-oxygenation.[5] However, this method of assessing pre-oxygenation would be impractical in actual ED patients who are critically ill and may not be able to fully participate in such a measurement. In addition, discontinuing a pre-oxygenation method to obtain a single breath EtO2 reading would be unethical as it would interfere with proper pre-oxygenation in a critically ill patient. A better method would be to examine end-tidal oxygen measurements from patients in real-time as they are being pre-oxygenated. This study will examine the use of a real time nasal cannula EtO2 sensor as compared to the gold standard of a single breath exhalation into a static sensor.

Introduction

We hypothesize that end-tidal oxygen (EtO2) could be continuously and reliably measured using a nasal cannula with a gas sampling line that is typically used to measure end-tidal CO2 (EtCO2) during pre-oxygenation in healthy volunteers. However, it is possible that high flows of oxygen that would be typically required for pre-oxygenation could distort patient measurements when placed underneath the oxygen mask. To our knowledge, no studies have examined this technique.

Use of the EtO2 real time reading from a nasal cannula could lead to improved pre-oxygenation for ED patients undergoing RSI by allowing clinicians to gauge the completeness of pre-oxygenation prior to starting the intubation procedure. Clinically, if a patient has a low EtO2 or ORI reading, this could prompt clinicians to delay the procedure until the patient can be better pre-oxygenated. This could lead to improved patient safety by decreasing the incidence of hypoxia during the intubation procedure that can lead to significant morbidity and mortality. Conversely, if the EtO2 is already at 90% or greater, the clinician may be able to start the intubation procedure sooner and not delay other critical interventions while waiting to further pre-oxygenate the patient.

3. **Objectives**:

Primary Objective: In healthy volunteers, how well does a real time nasal cannula EtO2 sensor correlate with a single breath exhaled EtO2 measurement?

4. **Study design and methods**:

Study Procedure

After screening procedures, participants will be ask to self report age, gender, height, and weight. Each participant will then perform a single breath EtO2 measurement to determine their own individual room air EtO2 measurement. They will also have a baseline measurement taken by the EtO2 nasal cannula sensor. Subjects will then be fitted for an appropriately sized non-invasive ventilator mask. Prior to the start of the study procedure, a nasal cannula EtO2 sensor will be placed on the participant's face with the non-invasive mask overlying the sensor. Participants will be randomized into each study arm after enrollment: the NRBM arm and the

NIV arm. Each participant will participate in the following treatment sequence. In addition to the study arm allocation, participants will be randomized to the order of their treatment sequence. After each treatment is completed, the participant will perform a single breath exhalation into a standard FeO2 sensor.

Group 1: NRBM Arm

#1 NRBM at 15 LPM for 3 minutes

#2 NRBM at 35 LPM for 3 minutes

#3 NRBM at flush rate (55 LPM) for 3 minutes, the maximal reading at the end of this trial will be recorded, then the study subject will be allowed to rest until their EtO2 returns to their baseline, then they will be placed back on NRBM at flush rate, allowed to rise to the maximal reading of the previous step, then do a single breath exhaled EtO2 measurement

Group 2: NIV arm

#1 NIV at 40% FiO2 for 3 minutes

#2 NIV at 70% FiO2 for 3 minutes

#3 NIV at 100% FiO2 for 3 minutes, the maximal reading at the end of this trial will be recorded, then the study subject will be allowed to rest until their EtO2 returns to their baseline, then they will be placed back on NIV at 100% FiO2, allowed to rise to the maximal reading of the previous step, then do a single breath exhaled EtO2 measurement

After each trial for #1 and #2 in each study arm, the study participants will be allowed to rest while breathing room air. Prior to the start of the next trial, each participant will perform a single breath EtO2 measurement to ensure they have returned to their baseline measurement. If the measurement is determined to be above their baseline, they will be allowed to rest until their single breath EtO2 measurement returns to its pre-intervention baseline. For trial #3 in each arm, the protocol will be followed as above so that the maximal reading can first be obtained to allow the completion of arm #3.

Risks and Discomforts

The risks to study participants would be no more than minimal risk. The most common risk to study participants would be discomfort from using the NRBM or NIV masks. Participants may experience claustrophobia or discomfort from the higher flows of oxygen and air. If participants cannot tolerate the NRBM or NIV mask, they can discontinue the study at any time by removing the NIV mask themselves or asking a study investigator to remove the mask.

The study's original PI and the author of this protocol (Dr. Stephen Carroll) has designed and helped to execute a similar study at his last institution that was similar in design to this study. This study involved placing healthy volunteers on a NIV mask with a nasal cannula

underneath the mask. All study subjects (64 in total) we able to tolerate the full study protocol without any adverse effects. This study has been published in a peer-reviewed journal.[7] The IRB approval letter designated the study as "no more than minimal risk" with an expedited review is included in the e-IRB submission as an appendix.

Randomization

Study subjects will be randomized by computer to their initial study arm (NRBM or NIV). Study subjects will then be randomized by computer to the order of oxygen flows/FiO2 levels delivered by the NRBM or NIV mask, respectively.

Data collection and storage procedures

All data will be collected on a standardized data collection form and entered into a secure database program (REDCAP) for data analysis. The PI, AI, and any study research personnel who assist with the study will have access to the database. Each subject will be assigned a subject number according to the order in which they were enrolled into the study. The data will be stored for a maximum of 3 years to ensure the ability to publish study results. After the data is stored for 3 years, it will be deleted. In addition, the study investigators will video record the screens displaying the EtO2 data to allow accurate data transcription. Once the data has been transcribed, these videos will be deleted. These videos will solely be focused on the video screen and will not capture the study subject's face or any other identifying features. These videos will only be identified by the assigned study subject number and will not contain any other identifying information.

Participant selection

This study will be conducted in healthy volunteers. Volunteers will be recruited from within the staff of the ED at Grady Memorial Hospital. We aim to enroll 104 participants- 52 in each study arm. Assuming a dropout rate of 10%, we will enroll a maximum of 116 patients. However, enrollment will terminate once 104 participants with a full data set have been enrolled.

Inclusion criteria (with justification in parentheses):

-Adults 18 years of age and older who are able to consent on their own without a legal representative (ability to consent)
-Self-identified as being in good health (ensuring healthy volunteers)
-Grossly normal dentition as judged by study investigators (may affect NIV mask seal)
-No self-reported symptoms of upper respiratory infection or other infectious process (ensuring healthy volunteers)
-No history of severe pulmonary disease or asthma that requires daily use of an inhaler (ensuring healthy volunteers)
-Females participants only: Self-reported to not be pregnant at time of study enrollment (for protection of an unborn child)

Exclusion criteria:

-Participant does not agree to study enrollment
-Participant cannot tolerate the entire course of non-invasive ventilation required to complete the study.
-Participant does not agree to the video recording of the oxygen monitor to ensure proper data transcription

Study subjects will be recruited from within the Department of Emergency Medicine at Grady Memorial Hospital and Emory University Hospital Midtown. Study participants will be drawn from a pool that will include nursing staff, paramedical staff, students, residents, and attending physicians.

Study subjects will be assessed for inclusion or exclusion criteria prior to starting the study. Study subjects will provide written informed consent after the study procedures have been explained to them and any questions are answered. No personally identifiable health information will be collected during study enrollment.

If a study subject wants to withdrawal from the study they can do so by notifying the study investigators at any time. If a study subject chooses to withdrawal, they will most likely do so due to intolerance of the NRBM or NIV mask. If this occurs, they can remove the NRBM or NIV mask themselves or request that a study investigator remove the NIV mask for them. The option to remove the mask themselves or request that a study investigator remove the mask for them will be made clear during the process of written informed consent.

Informed consent process

Each study participant will provide written informed consent for the study. After screening for inclusion or exclusion criteria, a study investigator will explain the study procedures in plain language. Study participants will then be allowed to ask any questions to be answered by the study investigator. If the study participant agrees to enrollment, they will be provided with the written informed consent document and be given sufficient time to read the document and ask any additional questions. The study procedures will not be implemented until the study participant signs the informed consent document.

A HIPAA authorization will be included in the text of the consent document for the study.

For student or resident participation, participation or non-participation will not have any effect on any grading or evaluation that they may receive during their rotation or training. For all other participants, participation or non-participation will not have any affect on any employee evaluation, salary, compensation, or continued employment with Grady Health System or Emory University.

In addition, no students or other trainees will be approached face to face for recruitment by the study personnel or their clinical supervisors. They will also not participate in the study during their clinical shifts and they will not be specifically targeted for enrollment. Students and other trainees will be recruited in a general fashion via emails to the department of emergency medicine and flyers placed in public areas of Grady Hospital and Emory University Hospital Midtown.

Study participant compensation

Study subjects will be compensated with a $20 Amazon Gift Card for their time once they are deemed to be eligible to participate in the study and have provided written informed consent. This study is anticipated to take approximately 45-60 minutes of the study subject's time to allow for written informed consent and all the study trial activities. If they choose to withdrawal prior to full study completion, they will keep the $20 gift card.

Statistical Analysis:

Power calculation

The study will be sufficiently powered to detect a 5% difference in ETO_2. Five percent was chosen because it equates to approximately 30 extra seconds of safe apnea time in an 80 kilogram male (5% X 2,400 ml/O2 consumption at 250 ml/min).[6] Based on a previous studies with similar study designs,[2,3] we estimated that the standard deviation of ETO_2 would be approximately 6.8%. Because six tests will be conducted, findings will be considered significant at the 0.0085 level (Sidak-corrected p value). These values were used to estimate the sample size required to achieve 80% power using Monte Carlo Simulations (10,000 samples) implemented in R v3.4.1. This analysis returned a total sample size of 104 (52 per arm). In order to account for an anticipated dropout rate of 10%, 116 participants will be enrolled. However, study enrollment will be terminated once 104 study subjects with complete data sets have been enrolled.

If a study participant cannot complete the entire protocol, their data will be excluded from the data analysis.

Missing Data

In the event of substantial missing data, data will be imputed using a multiple imputation procedure. The type of procedure and the number of imputed data sets will be determined by the amount of missing data and the pattern of missingness.

Data and Safety Monitoring and Reporting

Since this study does not involve any more than minimal risk to study participants, there will not be a pre-planned interim monitoring or data analysis.

While significant side effects and reportable events are not anticipated from the study, any significant side effects requiring medical treatment or reportable events will be immediately reported to the Emory IRB by the study's primary investigator.

Confidentiality

Study participant's inclusion in the study will be kept confidential. Study subjects will be assigned a study subject number at the beginning of the study. Study subjects will be asked to self report their age, sex, height, and weight which will be recorded onto the data forms. These data forms will not contain any other personally identifiable study subject information. Data from these forms will be transcribed into a secure database (REDCAP).

Video recordings of the monitor readings will be immediately deleted after they are transcribed onto the data forms, which will occur immediately at the end of each study procedure. Study subjects will be consented for these video recordings prior to the study. If they do not consent to these video recordings, they will not be allowed to enroll in the study.

3. References/bibliography

References:

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