JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research

Monitored anesthesia care with procedural sedation has increased dramatically over the past 15 years, driven by increased utilization in gastrointestinal endoscopy, cardiology (both interventional and electrophysiology), and interventional radiology. Despite the increase in the number of patients receiving procedural sedation, current monitors of respiratory depression are inadequate to determine the degree of anesthetic induced hypoventilation. Underappreciated hypoventilation puts patients at risk for hypoxia, respiratory arrest, cardiopulmonary arrest, and other adverse events. While pulse oximetry is an outstanding and required monitor of oxygen saturation, it is a poor monitor of ventilation in patients receiving supplemental oxygen. The American Society of Anesthesiologists Monitoring Standards recognizes the underlying contribution of hypoventilation to hypoxia and adverse events by mandating the use of end-tidal capnography for procedural sedation. While well intentioned, end-tidal capnography is helpful in determining respiratory rate, it appears to be insufficient for detection of hypoventilation during procedural sedation. In fact the quantitative value may paradoxically decrease as the degree of hypoventilation increases. Further, the mechanism of anesthetic induced hypoventilation during monitored anesthesia care with procedural sedation is not entirely understood or appreciated.

Fortunately, other FDA approved monitors are available that can non-invasively monitor additional respiratory parameters and hypoventilation. The ExSpiron™ respiratory monitor is an FDA-cleared device that allows acquisition of quantitative values of respiratory rate (RR) tidal volume (TV), and minute ventilation (MV), and has a signature pattern to identify episodes of airway obstruction (Respiratory Motion, Inc. Waltham, MA). Transcutaneous CO_2 ($PtcCO_2$) monitoring is a non-invasive method for continuous monitoring of overall ventilation that closely approximates arterial carbon dioxide values ($PaCO_2$) obtained from blood samples (SenTec, Bern, Switzerland). Further, processed electroencephalography (EEG) using bispectral index (BIS) is a non-invasive monitor that has been described as a marker for depth of anesthesia during general endotracheal anesthesia GETA and procedural sedation (Medtronic, Minneapolis, MN. Together, these devices will allow a more

precise understanding of the respiratory effects of monitored anesthesia care and procedural sedation.

This study will use this innovative combination of respiratory monitors to better understand the magnitude and mechanism of respiratory depression during MAC with procedural sedation at different anesthetic levels. For example, we will be able to distinguish the decrease in minute ventilation due to loss of motor tone and subsequent airway obstruction from that caused by decreased respiratory drive minute ventilation due to changes in tidal volume, respiratory rate, or both. Likewise, these devices have the potential to improve the monitoring of respiration and the quantification of hypoventilation, making it a potentially valuable tool for clinical care in the future, as well as further studies to determine anesthetic regimens that may cause less respiratory depression. Further, if the addition of CPAP does in fact alleviate obstruction and decrease hypoventilation, it is a potentially very important finding for patient care.

In addition, this study aims to explore a novel mechanism that may account for individual variability in the respiratory response to anesthesia. Short chain fatty acids are produced by the gut microbiome (non-pathological bacteria in the gastrointestinal tract). Low levels of these compounds have been associated with hypertension and obesity, as well as hypertension in people with sleep apnea. Receptors that are activated by these compounds are found in high concentration in the carotid body, where their activation appears to stimulate respiration. We will measure serum levels of short chain fatty acids, and hypothesize that lower concentrations will be associated with greater anesthesia induced respiratory depression and higher levels will be protective. If short chain fatty acids are shown to be associated with a protective affect on respiratory depression, this could open the door to an entirely new understanding of the mechanisms that contribute to respiratory depression during anesthesia, but also those involved with obstructive sleep apnea. In addition, it could raise the possibility that short chain fatty acids could be administered as a protective treatment.

2. Objectives (include all primary and secondary objectives)

Specific Aim 1: To test whether nasal CPAP reduces the incidence of hypoxia during procedural sedation with propofol as compared to usual care. Hypothesis: A randomized clinical trial of an intervention to reduce airway obstruction (nasal CPAP) will decrease the incidence of hypoxic events ($<90\% \geq 15s$) compared to usual care in patients undergoing procedural sedation.

Specific Aim 2: To determine the duration, magnitude and mechanism of hypoventilation and its association with hypoxia in subjects undergoing procedural sedation. Hypothesis: By determining minute ventilation, transcutaneous CO2 and sedation depth while measuring end-tidal CO2, it will be possible to relate ventilation to hypoxic events, sedation depth and airway obstruction. Further, reductions in the incidence of hypoxia in the intervention group will be consistent with the hypothesis that loss of airway motor tone underlies hypoventilation and associated hypoxia.

Specific Aim 3: To characterize the physiologic state when end-tidal capnography is insufficient for detecting hypoventilation. Hypothesis: The amplitude of the capnographic signal is not representative of the adequacy of ventilation due to artifact from loss of airway motor tone during procedural sedation.

Specific Aim 4: To determine if there short chain fatty acid serum concentration is protective for procedural sedation induced hypoventilation, obstruction and hypoxia: Hypothesis: Higher concentration

of short chain fatty acids will be reduce the risk of hypoventilation, obstruction, and hypoxia and suggests a link between respiratory function and gut microbiome.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

There has been an explosion in the number of anesthetics administered outside of traditional operating rooms in the last decade. The rise in such non-operating room anesthetics (NORA) has been driven by increased demand in gastrointestinal endoscopy (GE), interventional radiology, and cardiology.[1] Increased anesthesia support for GE procedures appears to be the primary driver for the rise in NORA.[1] The increase is huge – between 2003 and 2009, anesthesia support for GE for Medicare patients grew from 13.5% to 30.2%, while anesthesia support for patients undergoing GE procedures with private insurers increased from 13.6% to 35.5%.[2] In 2009, an estimated 18.6 million gastrointestinal endoscopies were performed in the United States, of which 6.9 million were upper, 11.5 million lower, and 228,000 biliary.[3] Together, these studies suggest that more than 6 million anesthetics were administered for GE in 2009. Further, previous projections have indicated that anesthesia services would be used in over half of all GE procedures by 2015.[4] These predictions appear to be reflected in reports of increased NORA for GE at tertiary medical centers.[5,6] In the endoscopy suite at the Johns Hopkins Hospital, nearly all GE procedures are performed with anesthesia involvement, with an increase in annual cases from from approximately 4000 in 2007 to nearly 12,000 in 2015.

Fundamentally, the shift to anesthesia involvement in gastrointestinal endoscopic procedures represents a change from gastroenterologist directed, nurse administered sedation with fentanyl and midazolam, to a propofol-based anesthetic.[7] This change has been driven by several factors, including patient preference and satisfaction, risk aversion on the part of the proceduralist, perception of better procedural conditions, and evidence of decreased length of stay in the post anesthesia care unit and faster throughput.[8,9] The use of propofol sedation compared to midazolam and fentanyl appears to be associated with deeper levels of anesthesia.[10] In fact, when propofol is used for procedural sedation, electroencephalographic monitoring such as BIS suggests anesthetic depth often associated with general anesthesia.[11] Some retrospective studies have suggested higher rates of complications with propofol-based anesthetics compared to midazolam and fentanyl, including cardiorespiratory arrest, aspiration, and hypoxia.[12] In contrast, other studies have suggested no difference or improved outcomes with anesthesia involvement, and patients were generally sicker with longer cases.[13,14]

The large and growing number of GE procedures with anesthesia services underlies the importance of delivering safe care, as even a low rate of sedation related adverse events may affect a large number of patients. In several retrospective studies, cardiopulmonary events occurred in up to 11.7/1000 events, and hypoxia was the most common.[13] While the full implication of mild transient hypoxia on outcomes is unknown, significant hypoventilation with hypercarbia and hypoxia commonly proceeds cardiopulmonary arrest.[15] Respiratory depression from oversedation is an important mechanism of patient injury during monitored anesthesia care.[16] The rate of hypoxia is considered as a marker for unsafe sedation practices in endoscopy suites.[17] However, the true rate of hypoxia associated with sedation for endoscopic procedures is unknown and ranges from 1% to 70% in the literature.[18,19,20] The variability may be related to adequacy of surveillance as well as differences in the definition of hypoxia. For instance, lower rates of hypoxia in manually and electronically recorded pulse oximetry data during clinical care have been reported.[21] A recent study from the Netherlands reported a hypoxia rate in average risk patients during sedation for colonoscopy without oxygen supplementation of 55.6%.[22] A recent study from Germany pseudorandomized patients undergoing upper, lower, or combined endoscopic procedures with propofolbased anesthesia to nasal cannula alone or with a nasopharyngeal airway and found rates of

hypoxia of 1.8% versus 13.5%.[23] In another study from the Cleveland Clinic evaluating the STOP-BANG sleep apnea scoring system, subjects with STOP-BANG score >3 had a rate of hypoxia of 16.9% versus 11.2% in the STOP-BANG score <3 group, but this did not reach significance in this underpowered study.[24] However, higher BMI was associated with more sedation-related adverse events (SRAE).

Hypoxia is related to both centrally mediated changes in respiratory drive caused by sedative drugs, direct effects of the anesthetic agents on motor function, and diminished airway tone due to sleep or sedation (change in state). Furthermore, sedative agents decrease airway tone and increase the risk of obstruction, while blunting the normal arousal that occurs in response to hypercarbia and hypoxia during obstruction events during natural sleep.[25,26] Obstructive sleep apnea and obesity are risk factors for airway obstruction during sedation.[14,25] Use of nasal CPAP has been demonstrated to improve ventilation, alleviate upper airway obstruction, and reverse hypoxia in women undergoing spinal anesthesia with sedation for gynecological procedures.[27] Continuous positive pressure stents the airway, alleviating the obstruction from oropharyngeal soft tissue that occurs during sleep and under sedation, and has been advocated in patients with obstructive sleep apnea on CPAP at home.[28] Positive pressure ventilation using a nasal mask has also been shown to be effective.[29] The Supernova mask (RMD medical, Tucson, AZ) is FDA approved commercially available nasal mask that can be attached to a standard anesthesia circuit or Jackson Reese, and allows for up to 30 l/min of oxygen delivery, making it convenient for use in procedural sedation. It can supply CPAP as well as supplemental positive pressure breaths by closing the mouth or applying gentle cephalad directed submandibular pressure to push close the oropharynx by approximation of the tongue and palate.

During general endotracheal anesthesia (GETA), airway obstruction is bypassed by the endotracheal tube and the closed system allows for minute ventilation to be continuously monitored and end tidal carbon dioxide ($EtCO_2$) generally approximates arterial carbon dioxide (PaCO2). During monitored anesthesia care, end tidal carbon dioxide ($EtCO_2$) monitoring is routinely utilized as a qualitative marker of respiratory rate, but quantitative evaluation to identify hypoventilation is usually not possible by nasal cannula or standard mask ("green mask). Likewise, minute ventilation is not routinely monitored. In fact, ETCO2 reading often decreases during hypoventilation with opioids and sedatives, while respiration paradoxically decreases (see figure, attached).[30] Still, ETCO2 monitoring remains an important measure of respiratory rate, and has been shown to decrease the rate of hypoxia during procedural sedation for colonoscopy from 32% to 18%.[31] Prevention of hypoxia by administering supplemental oxygen may blunt the potential increase in respiratory drive stimulated during opioid and sedative administration.[32] However, prevention of hypoxia during procedural sedation using oxygen allows for airway interventions prior to the onset of hypoxia when ventilation is being carefully monitored. Current standard of care for monitored anesthesia care with sedation includes use of qualitative $EtCO_2$ as a marker of respiration, but does not include quantitative monitoring of minute ventilation or the degree of hypoventilation.
Impedence based respiratory volume monitoring has been used to assess adequacy of ventilation and airway obstruction in patients undergoing endoscopic gastrointestinal procedures.[33,34] In fact, such studies also suggest that $EtCO_2$ often decreases as minute ventilation decreases. In this study, changes in minute ventilation from baseline, and episodes of upper airway obstruction will be assessed using the commercially available ExSpiron™ (Exspiron, Respiratory Motion Inc, Waltham MA). Previous studies using the ExSpiron™ have suggested that decreased minute ventilation during sedation for GE procedures is primarily due to decreased tidal volume rather than respiratory rate.[33] Transcutaneous carbon dioxide has proven to closely approximate to arterial carbon dioxide ($PaCO_2$), and in fact more closely reflects $PaCO_2$ then end tidal carbon dioxide ($EtCO_2$).[35] Transcutaneous carbon dioxide ($TcCO_2$) has been shown to closely correlate with $paCO_2$. After approximately 5 minutes of calibration time, it appears to track changes in $PaCO_2$ with a lag time of 30 seconds to 2 minutes. In our experience using the $TcCO_2$ monitor

for clinical application during jet ventilation, we have found the device to consistently track within 5 points of the $PaCO_2$. (Sentec, Therwil, Switzerland).

Depth of anesthesia using processed electroencephalography has been described as a marker for depth of anesthesia during GETA and MAC with sedation. Depth of anesthesia using bispectral index (BIS) has been relatively well established and is known to correlate well with other measures of depth of anesthesia.[36,37] We will use bispectral index (BIS) (Medtronic, Minneapolis, Minnesota) as a marker of state. In addition, all clinical data utilized in routine practice will be recorded, including drug dosing, method of drug administration, and length of stay in the recovery area.

Recently, alterations in the gut microbiome have been implicated in obesity, hypertension, obstructive sleep apnea induced hypertension, and airway smooth muscle tone that may relate to reactive airway disease.[38-40] In general, lower short chain fatty acid levels are associated with pathology, and higher levels appear to be

protective. Olfactory receptors located in vascular endothelium are activated by short chain fatty acids, causing smooth muscle relaxation, vasodilation, and protection from hypertension, with some feedback mechanisms that may prevent significant hypotension as well. Interestingly, these receptors are also highly expressed in the carotid body, where activation by short chain fatty acids increases respiratory drive.[41] This is an intriguing possible mechanism for individual variability in susceptibility to anesthesia induced hypoventilation and may also be a contributing mechanism for hypoventilation in patients with sleep apnea. We hypothesize that lower serum concentration of short chain fatty acids will be associated with more respiratory depression and higher levels will be protective. Further, we suspect that patients with known obstructive sleep apnea, hypertension, and high BMI will have lower short chain fatty acid levels.

This study is a randomized controlled trial comparing oxygen delivery by nasal mask with CPAP versus standard care (nasal cannula or standard facemask) during propofol-based sedation for GE procedures to reduce the incidence of hypoxia. The primary outcome will be the rate of oxygen desaturation below 90% for ≥15 seconds. In addition, secondary measures will include evaluation of mechanism and degree of respiratory depression associated with hypoxia and hypoventilation by characterizing changes in minute ventilation, tidal volume, and respiratory rate as well as the rate and degree of airway obstruction. We hypothesize that the addition of Nasal CPAP in the intervention arm will lead to decreased obstruction as positive pressure will stent open the obstructed airway. Depth of anesthesia will be monitored by BIS and we hypothesize that the degree of hypoventilation, obstruction, and will be significantly lower in the intervention arm compared to the control arm. Further, the depth of anesthesia will be independent of total propofol dose received. While the primary outcome in this study is hypoxia, we also seek to marry $ETCO_2$ with minute ventilation and transcutaneous CO_2 to better understand the total effects of sedation on respiration. Thus, the study will also serve to evaluate which mode(s) of respiratory monitoring might be the best possible intervention to enhance safety during procedural sedation. Further, we suspect that the amplitude of $ETCO_2$ will not predict the degree of respiratory depression seen with other monitors. In addition, we will measure serum short chain fatty acid concentrations as a predictor and possible mechanism for differences in individual variability in anesthesia induced respiratory depression.

4. Study Procedures

Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This study is a randomized controlled trial comparing oxygen delivery with nasal CPAP versus standard care (delivery via nasal cannula or standard facemask) during propofol-based sedation for endoscopic procedures. The primary outcome will be the rate of oxygen desaturation below 90% for ≥ 15 seconds. Secondary outcomes are the degree of hypoventilation measured by continuous transcutaneous carbon dioxide ($TcCO_2$), the change in minute ventilation (MV) and obstructive episodes measured by impedence-based respiratory volume monitoring, and depth of anesthesia measured by bispectral index (BIS) monitoring. The adequacy of standard $ETCO_2$ monitoring will also be assessed. In addition, all clinical data utilized in routine practice will be recorded, including drug dosing, method of drug administration, blood pressure changes, frequency of interruption of procedure for airway maneuvers or rescue, length of stay in the recovery area, and any complications that are identified.

Subjects will be recruited from the patient population scheduled for MAC with sedation for gastrointestinal endoscopic procedures at the Johns Hopkins Hospital Endoscopy Center on Zayed 2. Patients scheduled for colonoscopy, EGD (including EGD with biopsy, ultrasound, PEG

placement, or enteroscopy) or combined upper and lower endoscopic procedures predicted to last longer than 10 minutes and for which MAC with sedation is the planned anesthetic technique will

be considered for the study. A study team member will screen the endoscopy schedule for potential subjects. We will direct our recruitment to patients with documented OSA or a BMI ≥ 30, but we not limit it to just those patients. Written, informed consent will be obtained from interested eligible subjects or their representative.

As part of routine care, all patients undergoing MAC with sedation receive an IV in the preoperative area. During the placement of this IV up to 15 mL of blood will be collected for short chain fatty acids measurements and possibly the measurement of biomarkers and other compounds. The written consent form will include permission from the participant to store their blood for future research.

All subjects enrolled in the study will have research monitors placed on the skin in a similar fashion to the pads for ekg lead placement, with respiratory volume monitoring on the chest, BIS and $TcCO_2$ on the forehead. All enrolled subjects will be connected to the ExSpiron^{TM} monitor (Respiratory Motion, Inc., Waltham MA) and digital respiratory traces of MV, TV, and RR measurements will be collected on all 240 patients. The ExSpiron monitor uses an adhesive, latexfree, adjustable 5 sensor strip applied to the chest to measure the amount of air moving in and out of the lung in real time. Minute ventilation will also be correlated to transcutaneous CO_2 as measured by the SenTec Digital Monitor (SenTec AG, Therwil, Switzerland). Transcutaneous CO_2 (Ptc CO_2) monitoring provides a noninvasive technique allowing continuous monitoring of ventilation. It is based on arterialization of the capillary bed through the local application of heat and the use of Stow–Severinghaus electrodes. The sensor will be calibrated, applied to the patient's forehead, cheek, or chest, and warmed to a constant surface temperature of 42 °C. In adults, these temperatures are safe for up to 24h, and the procedures performed in this study are generally less than 2 hours. The BIS monitor is also an adhesive strip with 4 sensors applied to the subjects forehead.

All subjects will also have standard, routine monitors placed by the treating team, including blood pressure, ECG, pulse oximetry, and $EtCO_2$. Subjects will be randomized to either 1) receive oxygen by nasal mask (nCPAP) with CPAP of 10 mmHg or 2) standard oxygen therapy. Subjects randomized to nCPAP will have a nasal facemask (SuperNOVA) placed approximately 5 minutes prior to the procedural start. The mask attaches to the anesthesia circuit, oxygen flow will be set at 10 lpm, and the CPAP of 10 will be set by turning the "pop-off" valve to 10 mmHg. Subjects randomized to standard care will have oxygen delivered by nasal cannula or simple facemask with oxygen level set by the treating providers. The CPAP level of 10 will be chosen because previous studies suggest that 95% of airway obstruction can be alleviated with a CPAP of 7.1, and it is convenient marked on the anesthesia "pop-off" valve, ensuring standardization.[27] For the CPAP group, flow below 10 lpm will be allowed in cases in which the patient or provider does not tolerate higher flows. For practicality, providers and patients will not be blinded to the intervention because application of the nasal mask is obvious. While the clinical team will have access to all of the routine monitors, they will be blinded to the research monitor data, which will include $TcCO_2$ monitoring, respiratory volume monitoring (RVM), and BIS. Researchers analyzing the data will be blinded to the intervention.

All subjects will receive a routine propofol-based anesthetic per the treating clinical team. A study team member will record all airway maneuvers or interventions performed by the anesthesia team during the procedure, including changes in oxygen flow, ventilatory assistance, jaw thrust, or placement of an oral or nasal airway. Further, the duration of the endoscopic procedure and any anesthesia related interruptions will be recorded. The study duration will be entirely within the time period of the patients' visit to the endoscopy suite. All study monitors will be removed when the participants are discharged to home or transferred to the ward depending on the clinical routine or needs.

Each subject will be assigned a study number to allow connection of the demographic data and clinical characteristics for comparison with the physiological data. All analog data for vital signs will be digitized using a digital to analog converter and processed using commercially available software. Medication data and length of stay data will be collected directly from EPIC . Additionally, data relating to any respiratory events (decreased RR, oxygen saturation, airway obstruction, etc.) requiring intervention will be recorded. Raw data from the ExSpiron™ monitor, actigraph device, and transcutaneous monitor will be stored in a separate file with the file name being the study number assigned above. There will be no patient identifiers in these files.

a. Study duration and number of study visits required of research participants.
Enrollment and data collection will begin after IRB approval. For each subject, the study will be performed entirely within their visit to the endoscopy suite. No additional visits will be required of study participants.

b. Blinding, including justification for blinding or not blinding the trial, if applicable.
The clinical team will have access to all of the routine monitors, but they will be blinded to the research monitor data, which will include TcCO2 monitoring, respiratory volume monitoring (RVM), and BIS. For practicality, providers and patients will not be blinded to the intervention because application of the nasal mask is obvious. Researchers analyzing the data will be blinded to the intervention.

c. Justification of why participants will not receive routine care or will have current therapy stopped.
Except for the application of study monitors to the skin and nasal CPAP in the treatment group, all subjects will receive routine anesthesia care to facilitate the planned procedure. The procedure will not be effected by participation in the study.

d. Justification for inclusion of a placebo or non-treatment group. Not applicable

e. Definition of treatment failure or participant removal criteria.
If a case is aborted because of procedural problems and no anesthesia was provided or the duration of the procedure was too short to obtain data, the participant would meet criteria for removal from the study. However, if an anesthetic requires change to an alternate anesthesia plan (such as conversion to general anesthesia) this will be recorded in the analysis.

f. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
If a participant's participation ends prematurely, they will receive routine care.

5. Inclusion/Exclusion Criteria Inclusion Criteria

Adult patients (≥ 18 years of age) undergoing colonoscopy, EGD, EGD with biopsy and/or ultrasound, or combined upper and lower endoscopy procedure anticipated to last longer than 10 minutes in the Endoscopy Suite in the Sheikh Zayed Tower at the Johns Hopkins Hospital when the anesthetic plan is MAC with propofol-based anesthesia with a natural airway.

Exclusion Criteria

LVAD
Severe Pulmonary Hypertension (defined by the PI or co-investigators during the screening)
EF < 35%
Active CHF
Planned procedure is Balloon Enteroscopy, ERCP
Topical lidocaine administration
Pregnancy
Previous enrollment in this study

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The ExSpironTM is an FDA-approved device that allows acquisition of quantitative values of minute ventilation (MV) (Respiratory Motion, Inc. Waltham). Unlike currently utilized ECG derived RR, the device's detection algorithm has been tuned to identify not just the onset of a new breath (RR) but also to estimate the thoracic size changes to provide a measurement of TV.

Transcutaneous CO_2 (Ptc CO_2) monitoring provides a noninvasive technique allowing continuous monitoring of ventilation. It is based on arterialization of the capillary bed through the local application of heat and the use of Stow–Severinghaus electrodes. Transcutaneous CO_2 monitors have been used in patients as young as neonates and a good correlation between Ptc CO_2 and $PaCO_2$ has been found in adults and children. (Berkenbosch JW, Tobias JD. Crit Care Med 2002 30:1024–1027. Herrejo´n A, Inchaurraga I, et al. Arch Bronconeumol 2006 42:225–229). The BIS monitor is an FDA approved, noninvasive monitor that can provide a validated monitor for depth of anesthesia and sedation.

The SuperNova^{TM} is an FDA approved nasal anesthesia mask that can generate CPAP to maintain airway patency, provide ventilator support, and provide rescue nasal ventilation during procedural sedation and during the perioperative period. The most likely risk is a red mark on the face from the mask, dry nose and mouth, and the very unlikely risk of nose bleed. (In fact, a common rescue during standard therapy is to place a nasopharyngeal airway, which carries a higher risk of nose bleed). CPAP and ventilator interventions associated with the nasal mask carry similar risks to interventions that may be required in patients undergoing sedation who require additional ventilator support.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. Not applicable

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. Not applicable

7. Study Statistics

a. Primary outcome variable.

The primary outcome will be the rate of hypoxia below 90% for ≥ 15 seconds.

b. Secondary outcome variables. Secondary outcomes will include change in respiratory parameters (tidal volume, respiratory rate, minute ventilation, obstructive events), hypoventilation by $TcCO_2$, $EtCO_2$, and depth of anesthesia by BIS, as well as demographic differneces. Demographic information to the occurrence of hypoxic events will be analyzed with logistic regression.

Statistical plan including sample size justification and interim data analysis.

Power analysis is based on a previous German study in the literature, of patients undergoing upper and lower endoscopy with hypoxia rates of 13.5% with standard care and 1.8% with application of nasopharyngeal airway. Using these figures to perform a power analysis for the primary outcome of hypoxia bellow 90%, with alpha 0.05 and power of 0.9, approximately 109 subjects in each arm or a total of 218 subjects will be needed. In order to obtain 109 completed subjects in each arm and to allow for those participants with incomplete datasets (e.g. monitor failure), we will enroll 120 subjects in each arm and a total of 240 subjects.

Frequency data will be analyzed with Fisher's Exact Test, ordered categorical data will be analyzed with the rank sum test, and continuous data will be analyzed with regression or equivalent techniques. Therefore, our primary outcome as to the incidence of hypoxia in each arm of the study will be determined using Fisher's exact test. All time series data from multiple sources will be aligned using the associated time stamp with the aid of the program data manipulation capabilities in Mathematica 11. Longitudinal analysis will be performed using a mixed model approach, initially with random intercepts alone, with the addition of nonlinear terms and interaction as indicated by the resulting model. Throughout, findings will be considered significant for $p < 0.05$ and p values will be determined using two-sided tests. Statistical analysis will be performed with the aid of Stata 13. An analysis will be performed after the first 20 subjects to ensure complete data collection and to run a batched analysis of SCFA to evaluate this aim. An interim data analysis will be done after ~120 subjects have been enrolled.

c. Early stopping rules.

Stopping will be considered if the intervention shows clear benefit at the midpoint of the study, or if it clearly shows no benefit.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency. All subjects will have, as a part of routine care, 5 ECG pads. The ExSpiron™ padset adds no more risk to the care of the subjects than does the 5 ECG pads routinely applied to the chest. The BIS padset is also very similar to the ECG pads, but will be placed on the forehead.

In the past, there was a risk of discomfort or skin burning in infants with the use of transcutaneous CO_2 sensors. However, current monitoring technology differs from previous sensors in the use of lower temperatures (42 °C as opposed to 45–47 °C) which has been shown to dramatically decrease the risk for skin burning (Storre JH, Steurer B, et al. CHEST 132:1810–1816). In adults, the

recommendation by the manufacturer is to check the site every 24 hours; however, for purposes of this study, sensors will be in place for significantly shorter period of time

The SuperNova^{TM} is a nasal anesthesia mask that can generate CPAP to maintain airway patency, provide ventilator support, and provide rescue nasal ventilation during procedural sedation and perioperative period. The most likely risk is a red mark on the face from the mask. Dry nose and mouth may occur, as can dry eyes, and a very unlikely risk of nose bleed. (In fact, a common rescue during standard therapy is to place a nasopharyngeal airway, which carries a higher risk of nose bleed). CPAP and ventilator interventions associated with the nasal mask carry similar risks to interventions that may be required in patients undergoing sedation who require additional ventilator support. b. Steps taken to minimize the risks.
Transcutaneous CO_2 sensors will be maintained and operated on the same site for a maximum 8 hours after which the site will be assessed for any signs of irritation and the monitor will be moved or removed if indicated.

Careful placement of the Supernova mask will be performed and the fit adjusted as needed. c.

Plan for reporting unanticipated problems or study deviations.

If transcutaneous CO_2 sensor sites demonstrate any signs of irritation, the sensor will be moved or monitoring discontinued as indicated.

Any unanticipated problem or study deviation will be reported to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

This study carries a low risk of loss of confidentiality. Multiple safeguards are in place to protect the confidentiality of the medical and demographic data. Each patient will be assigned a randomly generated number that will be linked to the medical record number. This file will be stored in a password protected spreadsheet and backed up to a network drive managed by the Department of Anesthesiology and Critical Care Medicine. Demographic and clinical data will be only linked to the random study number.

e. Financial risks to the participants. None

9. Benefits

a. Description of the probable benefits for the participant and for society.
This study may provide no benefit to any particular patient.

The study may benefit society if a better method of delivering oxygen is demonstrated for a procedure that is performed in millions of patients every year. Further, the study may help us to better understand how patients breathe under anesthesia, which may help us to improve delivery of anesthesia care in the future.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol. None

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will no costs for the monitors (the hospital has a separate supply) or the SuperNova masks used in the treatment arm of this study. Revolutionary Medical Devices will provide the SuperNova masks.

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