High Velocity Nasal Insufflation (Hi-VNI) Use in Upper Airway Surgery

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Study Summary

Title	**High Velocity Nasal Insufflation (Hi-VNI) Use in Upper Airway Surgery**
Short Title	Hi-VNI Use in Upper Airway Surgery
IRB Number	834412
Methodology	Prospective, interventional, pilot study
Study Duration	1 year
Study Center	Single center (University of Pennsylvania)
Objectives	• To establish the efficacy of Hi-VNI in upper airway surgery from the anesthesiologist's and surgeon's perspectives • To describe the ideal patient and the ideal pathology as well as suitable clinical scenarios when Hi-VNI should be selected
Number of Subjects	100
Main Inclusion and Exclusion Criteria	Inclusion criteria: Adult patients who are scheduled to undergo elective upper airway surgery at Penn. Exclusion criteria: All patients with underlying medical conditions in which brief periods of hypoxemia or hypercarbia are not well tolerated will be excluded. Patients in whom delivery of air with oxygen via nasal passages is contraindicated will be excluded. • Coronary artery disease • Severe heart failure with EF < 40% or implanted ICD • Pulmonary hypertension or pulmonary fibrosis • History of increased intracranial pressure • History of skull base or intracranial surgery • Severe nasal obstruction • Extremely low or extremely high BMI (BMI <16 or >40) • Patients at high risk for aspiration • Patients taken to OR for urgent or emergent upper airway surgery
Intervention	This study will involve use of Hi-VNI device as a primary or adjunct method for oxygenation.
Statistical Methodology	Mann-Whitney U test or Student's t-test and Kruskal-Wallis or ANOVA test will be used depending on the data distribution and the number of variables.
Data and Safety Monitoring Plan	The PI and sub-Is for this study will be responsible for the safety of the subjects enrolled into this study.

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Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable federal and state laws and regulations.

1 Introduction

The most challenging aspects of laryngeal and laryngotracheal procedures are difficulty of exposure and airway management. These procedures require use of microlaryngeal instruments through a small lumen of a rigid laryngoscope, and are oftentimes difficult to perform with a standard endotracheal tube in place. Similarly, when performing endoscopic evaluation of the trachea, access to the space and visualization of the entire 360-degree view of the trachea is crucial.

To overcome these challenges, a number of techniques for oxygen delivery have evolved over time. Among them are use of a small endotracheal tube, use of jet ventilation and intermittent apnea with periodic removal of the endotracheal tube. The aforementioned methods of airway management carry inherent risks of airway injury,[1,2] can be accompanied by brief periods of hypoxia or hypercarbia, and can sometimes lead to tenuous airway management scenarios for both the surgeon and the anesthesiologist when clear communication and familiarity with the airway management plan during the procedure are sub-optimal. For this reason, there is an ongoing search for acceptable solutions to minimize these risks during upper airway surgery.

One of the newly emerging advanced oxygenation techniques, also known as Hi-VNI (High Velocity Nasal Insufflation), allows for delivery of humidified oxygen through a specialized high-flow nasal cannula at rates of up to 40 l/min.[1,2] This non-invasive high flow respiratory support system is currently being used in the treatment of respiratory failure in both adult and pediatric patients. This technique provides sustained oxygenation due to reduction in airway resistance, a build-up of airway pressure with oxygen-rich gas and active gas exchange, which lead to flushing of anatomic dead space, and delivery of oxygen into the lungs.[3–5] This oxygenation technique can be used both in spontaneously breathing patients[6] and under apneic conditions,[7,8] while providing an unobstructed surgical view with the glottis, subglottis and trachea fully accessible for instrumentation.

The goal of this study is to establish the efficacy of Hi-VNI in upper airway surgery, to document the advantages and disadvantages of this technique from the standpoint of the airway surgeon and the anesthesiologist, and to provide more information about the optimal patient and airway pathology as well as suitable clinical scenarios when Hi-VNI device can be used for oxygenation during upper airway surgery. We hypothesize that in appropriate clinical situations, Hi-VNI can ease airway management, shorten case duration, and provide superior operating conditions including space for instrumentation during upper aerodigestive tract procedures.

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1.1 Background and Relevant Literature

Upper airway surgery is performed to treat a number of laryngeal and laryngotracheal conditions, many of which require an unobstructed view of the glottis, the subglottis, and the trachea. Various techniques of airway management have evolved over time to meet these requirements. These techniques include use of a small size endotracheal tube, intermittent apnea (periods with no breathing or oxygenation) during periodic removal of the endotracheal tube, and jet ventilation. The aforementioned methods of airway management allow for completion of the surgical procedures in the airway, but carry inherent risks of airway injury,[7,8] can be accompanied by periods of hypoxia or hypercarbia, and can sometimes lead to tenuous airway management scenarios.

Traditionally, before endotracheal intubation during surgical procedures, pre-oxygenation with a facemask is combined with apneic oxygenation via nasal cannula at rates of up to 15 mL/min. Apneic oxygenation with nasal cannula prolongs the safe apnea time, defined as the apnea time before desaturation. Recent advances in the field of anesthesia and oxygenation techniques introduced the Hi-VNI (High Velocity Nasal Insufflation) oxygenation technique. Hi-VNI technology has been utilized in cases of spontaneously breathing[6,2] or apneic patients.[7,8] Hi-flow nasal oxygen has been advocated to improve safety in bridging oxygenation of high-risk patients during apnea induced for urgent or emergent intubation[8–10]. Prior studies suggest that it prolongs the safe apnea time in physiologically fragile patients who cannot be ventilated by facemask due to risk of aspiration or challenging airway anatomy.

Our current approach in upper airway surgical procedures employs high-frequency jet ventilation (HFJV) or intubation with a small size endotracheal tube. In upper airway surgery, Hi-VNI oxygenation offers the advantage of an unimpeded and more stationary surgical view, while avoiding the risk of barotrauma when compared to jet “ventilation”,[9] and can deliver oxygenation in severe cases of airway obstruction such as cases of laryngotracheal stenosis when passage of the endotracheal tube or insertion of the jet ventilation cannula is difficult.[6] Hi-VNI may be advantageous as it produces less field motion when compared to HFJV, requires less technical expertise of the operator (requires a simple adjustment to titrate the rate of flow and oxygen content of the delivered humidified gas), does not entail instrumentation of the airway with a HFJV catheter or endotracheal tube, is not associated with the risk of barotrauma sometimes seen with HFJV, and allows for continuous oxygenation (HFJV needs to be paused during certain parts of the procedure to allow for a motionless field).

Most upper airway procedures we perform are short duration procedures and can be completed under apneic conditions or under the conditions of intermittent apnea if the safe apnea time is extended. Multiple recent case reports and small case series described instances where Hi-VNI-type devices extended the safe apnea time and improved patient safety. Wong et al. demonstrated that use of high-flow nasal oxygenation maintained the safe apnea time 40% longer (mean difference of 76 sec) when compared to facemask ventilation in morbidly obese patients (case series of 40 patients).[13] Lee and Quek described a case report of a morbidly obese patient (BMI of 40) undergoing a short laryngeal procedure (pan-endoscopy and vocal cord biopsy) with Hi-VNI providing adequate oxygenation without a need for adjunct methods of oxygenation/ventilation.[14] Hi-VNI has been recommended for use in

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critically ill patients during intubation in the ICU to prolong the safe apnea time and to help avoid emergent cricothyrotomy and tracheotomy.[12] Other studies described the benefits of high-flow nasal oxygenation in patients with respiratory distress requiring emergent intubation in the Emergency Department[4,5] This literature supports the concept that Hi-VNI devices can be used in apneic conditions to maintain adequate oxygenation.

We performed eight short cases of microlaryngeal surgery using Hi-VNI device at our institution, and noted better access to the glottis and the subglottic area with improved oxygenation and delay in desaturation under apneic conditions. These results and current literature on this technique call for further investigation of Hi-VNI use during upper airway surgery to provide additional information to the airway surgeon and the anesthesiologist regarding the most suitable patient and clinical scenario for its use based on the physiologic changes that occur when Hi-VNI is used for oxygenation.

Preliminary investigations published thus far provide some information about the physiologic changes that take place during Hi-VNI oxygenation under apnea. Ebeling et. al. described three cases of laryngeal and laryngotracheal surgery performed using Hi-VNI oxygenation with SpO2 maintained about 97% in all three cases, although their measured rise in pCO2 after 15 minutes of apnea, was slightly higher than previously noted.[8] Other studies documented use of this oxygenation technique with prolonged apnea without desaturation of up to 65 minutes during continuous endoscopic procedures[1,10] or in pediatric laryngeal surgery.[11] Lyons et al. in their series of 28 patients undergoing laryngotracheal procedures with high-flow nasal oxygenation as a sole oxygenation method showed that only 4 patients had brief desaturations (<2 min) to the levels of SpO2 85-90% supporting use of Hi-VNI during laryngotracheal procedures.[1] None of the studies included here reported adverse events related to Hi-VNI use, and in most instances the authors reported that Hi-VNI device was used as a sole method of oxygenation and provided adequate support. Our study will help address some of the limitations in the currently available knowledge about the use of Hi-VNI in surgical procedures of the upper aerodigestive tract and will contribute to the growing body of literature in this rapidly evolving area. Moreover, this study will help document the advantages and the disadvantages of Hi-VNI use from the standpoint of the upper airway surgeon and the anesthesiologist.

2 Study Objectives

The overall objectives for this study are to establish the efficacy of Hi-VNI in upper airway surgery from the anesthesiologist's and surgeon's perspectives, and to describe the ideal patient and the ideal pathology as well as suitable clinical scenarios when this oxygenation technique should be selected. This study will not change labeling of the Hi-VNI Precision Flow device by the Vapotherm and is not intended to change marketing claims of the manufacturer pertaining to this device.

2.1 Primary Objective

To evaluate Hi-VNI use for airway management and oxygenation in upper airway surgery from the anesthesiologist's and the surgeon's perspective with the specific focus on:

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- Physiologic changes during Hi-VNI use in apneic and spontaneously breathing patients such as maintenance of SpO2, changes in TcpCO2 (transcutaneous CO2) levels, and changes in vital signs, namely heart rate and blood pressure.

2.2 Secondary Objectives

To collect clinical information about the effect of Hi-VNI use on procedure duration with the specific focus on:

- The effect of this technique on the duration of the induction phase of anesthesia, surgical procedure duration, and the duration of emergence from anesthesia
- Ease of use and any intra-operative and post-operative difficulties that may arise from use of this oxygenation technique

3 Investigational Plan

3.1 General Design

This is a prospective, interventional, pilot study that will describe the select cases of upper aerodigestive tract surgery performed at our institution with use of the Hi-VNI device. Data captured will be analyzed with a goal of determining the efficacy of this oxygenation technique for upper airway surgery. We will also collect useful clinical information about the most optimal clinical scenarios for use of this technique based on the cases in our data sample that will demonstrate successful case completion without a need for adjunct oxygenation techniques aside from Hi-VNI such as jet ventilation or endotracheal intubation.

3.2 Allocation to Interventional Group

All subjects included in this study will undergo the same intervention, defined as the use of Hi-VNI as primary or adjunct oxygenation technique.

3.3 Study Measures

After all of the eligibility criteria have been checked and a written informed consent has been signed by the patient, the recruited study participant's records will be reviewed and pertinent information about the patient's past medical/surgical history will be recorded, including age, sex, weight, height, BMI, and other relevant information.

All patients will receive preoperative evaluation according to the guidelines established by the American Society of Anesthesia (ASA). If according to the ASA guidelines the patient requires a pre-operative EKG or other testing, the testing will be conducted prior to arrival in the preoperative area for a scheduled surgery. This is a routine sequence of events for all surgical patients, where they receive a preoperative physical exam and evaluation needed for medical clearance prior to surgery. Each patient will be evaluated by the surgical and anesthesia teams as part of the routine sequence of events for any surgical patient. All patients will have a full set of vitals taken, and will be seen by the nurse, anesthesia and surgical teams in the preoperative area.

Standard anesthesia monitoring during surgery will include EKG, blood pressure, SpO2 measured using standard anesthesia equipment used at our institution, transcutaneous pCO2

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levels (TcpCO2) measured using a SenTec transcutaneous monitor applied on the right or left upper arm prior to induction, EEG (using BIS monitor), and body temperature. We plan to use propofol and remifentanil without muscle relaxation as the primary anesthetic for all study cases. We do not define a maximum time for Hi-VNI use during the procedure. We anticipate that most of the study cases will be done within 20 minutes of the surgeon beginning the first step of the procedure. The anesthesia staff during the cases enrolled in this study will be limited to the sub-Is for this study (Drs. Atkins, Ayubcha, and Gavrin), who received an in-service training by the manufacturer of Vapotherm Precision Flow device, and have clinical expertise in use of this device in proposed settings. Both sub-Is are also familiar with the use of SenTec monitor during anesthesia, and will receive a detailed overview on how the device functions from a representative of SenTec before the study begins. They will be present in the OR during the study cases. Additional anesthesia team members including anesthesia residents, SRNAs and CRNAs will be required to read provided device manuals and study pathways/protocols before they participate in the care of the enrolled patients. The entire team including the circulator and the scrub tech, the surgical team, the anesthesia team will go over the use, the contraindications and hazards of the device use for Hi-VNI Precision Flow and SenTec monitor, the parameters that may prompt rescue ventilation and the steps to take if laser or cautery will be required. All staff members involved in the study cases will also review the airway fire protocol.

We intend to de-nitrogenate in the standard fashion with a face-mask. All patients will receive preoxygenation with bag-mask to ensure mask ventilation can be performed successfully during the case if needed and to determine end-tidal CO2. All patients who are successfully bag-masked during the induction phase will have disposable nasal cannula prongs placed to proceed with Hi-VNI use after the induction and the trial of bag-masking. If mask ventilation during the induction phase is successful, the anesthesia team will proceed with oxygenation via Hi-VNI device at a maximum rate of flow of 40 L/min and FiO2 of 100%. The rate of flow will remain at the maximum setting of 40 L/min throughout the case, and will not be adjusted at any point. If mask ventilation during the induction phase is unsuccessful, the anesthesia team will intubate the patient or HFJV will be initiated after exposure of the glottis by the airway surgeon as currently practiced, and this patient will be excluded from the study.

Transcutaneous CO2 is ideal for monitoring during apneic procedures with Hi-VNI since it provides a continuous trend of CO2 level and does not require a closed system (such as vent circuit attached to the endotracheal tube or a mask device). Prior studies reported no difference between transcutaneous CO2 levels and arterial CO2 levels during apneic procedures on the upper airway with Hi-VNI use[13] and when the correlation between arterial and transcutaneous CO2 was measured in healthy volunteers.[16] Transcutaneous CO2 correlated with arterial CO2 irrespective of BMI or sensor position further supporting its use in our study.[16] Since the measurement of the transcutaneous O2 is still considered experimental, and its correlation with the patient's oxygenation state has not been described in the literature, we will not use this parameter in our study. Based on our initial clinical experience and the experience of our colleagues at other institutions with TcpCO2 monitor use during general

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anesthesia, it is evident that end-tidal CO2 deviates from the level of TcpCO2 measured by the TcpCO2 monitor. We plan to establish a gradient between the value of end-tidal CO2 and the value of TcpCO2 in the beginning of each case, while the patient is being pre-oxygenated with a bag-mask. This baseline gradient will be used to determine the level of TcpCO2 adequate for continuous use of Hi-VNI during the case.

The Hi-VNI device will be used during the surgical procedure with continuous monitoring by anesthesia team. If at any point the SpO2 drops below 90% or TpCO2 minus the baseline gradient value rises above 55 mmHg, the airway surgeon and the anesthesiologist will stop the procedure and immediately switch to an alternate means of oxygenation by placing an HFJV cannula or a small-sized endotracheal tube through the laryngoscope into the glottis/trachea (a step performed in the beginning of the case if HFJV or endotracheal intubation are selected as primary methods of oxygenation during the case). These levels of TcpCO2 were not previously correlated clinically with PaCO2, and therefore should be avoided when using Hi-VNI system.

A total of 5 breaths will be administered via the endotracheal tube to determine the ETCO2 reading. If the ETCO2 reading is above 60 mmHg, the patient will be ventilated via the endotracheal tube. In other words, continuous monitoring will ensure that clinically significant hypoxia or hypercarbia (defined as SpO2 level below 90% or ETCO2 levels above 60 mm/Hg) that could eventually lead to adverse events if not promptly corrected will always be avoided by immediate switch to alternate means of oxygenation. HFJV equipment, a small-sized endotracheal tube, and all standard operating room airway and resuscitation equipment will be available as is the current standard during each case to allow for safe use of Hi-VNI and to prepare for the cases in which alternate means of oxygenation may be required.

All precautions will be taken to prevent vital sign changes that affect the accuracy of TcpCO2 measurements including changes in blood pressure, abnormal heart rhythm, or body temperature changes. Warming blankets will be used to avoid hypothermia. If a patient develops a transient arrhythmia or hypotension requiring vasopressor administration during the procedure, which can cause erroneous SpO2 and inaccurate TcpCO2, the patient will be intubated and the procedure will be completed with oxygenation/ventilation via the endotracheal tube. If the procedure cannot be performed with the endotracheal tube in place, the procedure will be aborted. If the arrhythmia persists, or if the nature of the arrhythmia is considered to warrant procedure termination, the procedure will be aborted. Additionally, if use of Hi-VNI support extends beyond 20 minutes, a blood sample will be drawn to evaluate CO2 level (PaCO2 or PvCO2). If the blood sample collection cannot be done, the patient will be intubated and ETCO2 will be measured.

If at any point during the procedure, a bleeding is encountered that requires cautery, the team will switch to an endotracheal tube to prevent aspiration of blood into the airway and to allow for appropriate hemostasis with use of cautery. If at any point during the procedure, it will become evident that the laser use is necessary, the team will switch to an alternate means of oxygenation. Standard practices currently in place to avoid airway fire will be used if the case demands use of electrocautery or laser. These practices will be implemented immediately once it becomes evident that either laser or electrocautery will be used. If laser or electrocautery will be used to control the bleeding during the case, following an endotracheal

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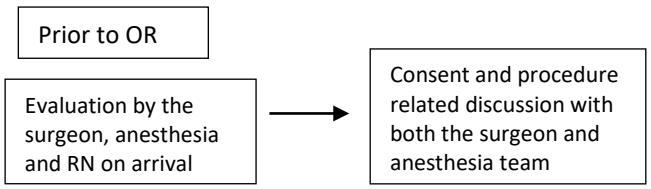
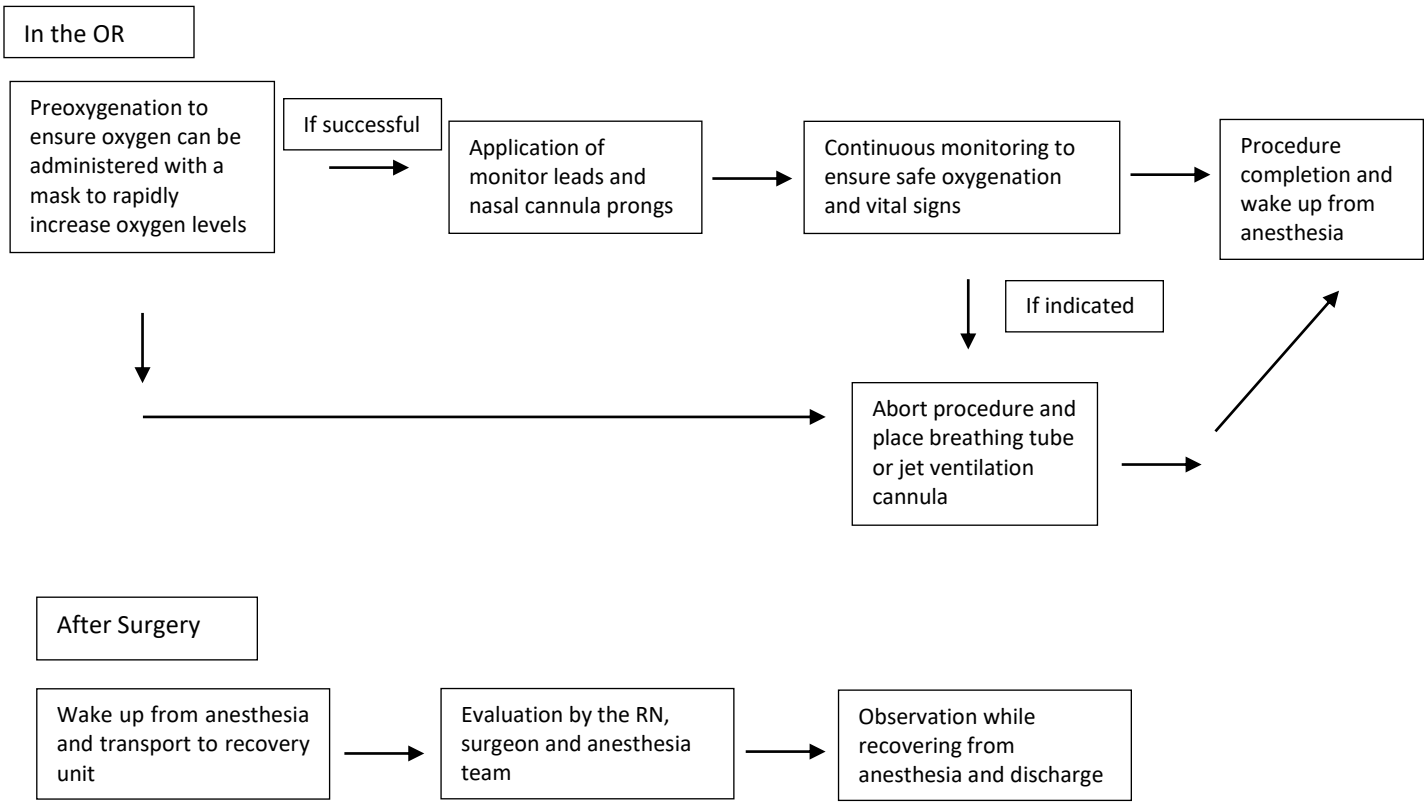
intubation, appropriate washout of residual oxygen will take place per routine protocol, and the laser or cautery will not be used until FiO2 levels reach the values below 21%. All standard fire precautions will be used and the oropharynx will be suctioned to remove any potential residual oxygen excess. All cases will be screened prior to enrollment into the study to avoid inclusion of the cases with high risk of large-volume bleeding requiring cautery or with a need for laser use during the procedure.

Any upper airway procedure we perform begins with direct laryngoscopy and the exposure of the glottic airway with a laryngoscope. With the exposed view of the vocal cords/glottic opening, the exchange step of endotracheal intubation or placement of the HFJV cannula takes a few seconds. The surgical and anesthesia staff assigned to these cases are familiar with the exchange from one mode of oxygenation to another since this is commonly performed for these cases. After performing a portion or the entire case with HFJV, the team generally elects to intubate the patient for the final steps of the surgical case or for emergence from anesthesia. In cases where HVNI is used, the surgeon and anesthesiologist team will then decide if the patient will continue to receive oxygenation through the nasal cannula, get mask ventilated, or get intubated. Investigators for this study do not anticipate any additional risks to the patient or significant additional time needed to complete these procedures during this study, even in the cases where use of Hi-VNI alone is insufficient.

All surgical aspects of the case will be captured using video recording, which is standard for all upper airway surgeries at our institution performed with use of an endoscope or a microscope. A review of the video recordings for the cases included in the study will help us better understand how tubeless surgical space impacts the length of the case (from the time laryngeal exposure is visualized to the end of the case) and to visually document the airway pathology treated with Hi-VNI. The duration of induction, the procedure itself and the emergence from anesthesia will be measured. Post-operative recovery of each participant will be assessed from the standpoint of any airway related complications, prolonged drowsiness or other complications pertinent to this study. Additional information about the ease of Hi-VNI use and any difficulties encountered during the surgical case will be recorded. Patients will also be asked to rate the comfort of the procedure including sore throat and irritation, which is anticipated to be less with the HVNI technique.

Schedule of events:





3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary endpoint for this study will be case completion rate without alternative mode of oxygenation. In other words, for each case, the ability to complete the surgical procedure with use of only Hi-VNI device for oxygenation will be assessed.

3.4.2 Secondary Study Endpoints

The secondary endpoints for the study will be the total case duration (induction to end of surgery), the time from the end of the case to emergence from anesthesia, nadir SpO2, peak TcpCO2, and rate of change in TcpCO2 (transcutaneous CO2).

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

The subject's participation in this study will be limited to the time of their upper airway surgery and the time needed for post-operative recovery. No long-term follow-up will be conducted for this study.

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4.2 Total Number of Subjects and Sites

We estimate that 100 subjects will be recruited for this study. Penn will be the only study site.

4.3 Inclusion Criteria

Our study population will include adult patients (22 years old or older) who are scheduled to undergo upper airway surgery at our institution with the airway pathology that will require surgical interventions which could potentially benefit from a tubeless surgical field. The airway pathology located directly at the site of the endotracheal tube placement (supraglottis, glottis, subglottis, and proximal trachea) will benefit from a tubeless surgical field.

- Patients must be able to read and understand English
- Participants must sign the informed consent form
- The surgical case must be a scheduled elective case and not performed as an urgent or emergent case

4.4 Exclusion Criteria

All patients with underlying medical conditions in which periods of hypoxemia or hypercarbia are not well tolerated will be excluded. Patients in whom delivery of air with oxygen via nasal passages is contraindicated will be excluded. The manufacturer's guidelines for Hi-VNI device use will be followed. The exclusion criteria will be defined as follows:

- Pregnancy (at our institution, all female patients of childbearing age receive a pregnancy test clinically prior to surgery as part of SOC)
- Coronary artery disease or carotid/vertebral artery stenosis
- Severe heart failure with EF < 20% or implanted ICD
- Pulmonary hypertension or pulmonary fibrosis
- History of increased intracranial pressure
- History of skull base or intracranial surgery
- Severe nasal obstruction
- Extremely low or extremely high BMI (BMI < 16 kg/m^2 or BMI > 40 kg/m^2)
- Baseline home O2 or Baseline SpO2 < 90%
- Airway pathology requiring laser use for surgical management
- Airway pathology requiring surgical intervention with high risk of large-volume bleeding
- Airway pathology requiring use of cautery throughout the procedure
- High risk of aspiration during the procedure as determined by the patient evaluation and review of prior medical history (history of gastrointestinal obstruction, prior esophageal procedures, esophageal cancer, hiatal hernia, incoordination of swallowing and respiration, class III obesity defined as BMI>40)
- Patients who are taken to the OR for an urgent or emergent upper airway surgery

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4.5 Subject Recruitment

Potential study participants will be identified using the surgical schedule and/or clinic schedule, and will be invited to participate using a standard informed consent form. Consent will be obtained by an Investigator (physician). Privacy will be ensured by discussing the study and the patient's disease within a private room in the clinic or in the pre-operative unit area, where they are unlikely to be overheard. Patients will be given ample time to read the consent form, discuss the study, ask questions, consider participation, and make an informed decision.

All potential participants will be provided with a short description of the Hi-VNI technique and the reasons for use of this technique during their surgical procedure. The subjects will have an opportunity to ask their airway surgeon (the PI) and their anesthesiologist (the sub-Is) about the reasons for selection of this airway management technique and any potential alternatives as well as the risks and benefits of its use during their airway procedure. The subjects will be enrolled into the study only after their consent is obtained and all of their questions about Hi-VNI have been answered.

4.6 Vulnerable Populations

There are no children or adolescents in this study, and all adult subjects will be competent to give consent. Negative pregnancy test (administered clinically, per standard of care) is one of the requirements for all adult female patients of reproductive age who are scheduled for surgical procedure at our institution, and pregnant women will be excluded from this study. Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

5 Study Procedures

Please see section 3.3.

5.1 Screening

The PI will identify eligible participants for this study using the surgical schedule and/or clinic schedule. The subject’s eligibility will be determined based on the type of the airway pathology, the type of planned surgical procedure and the exclusion criteria already described in Section 4.4 of this protocol. Additionally, the anesthesia team will make sure at the beginning of each case that adequate mask ventilation can be performed on each patient who consents to participate in the procedure to ensure that during the procedure the anesthesia team can safely switch to alternate modes of oxygenation.

5.2 Study Intervention Phase

All information needed for this study will be recorded during the upper airway surgical procedure and immediately after the surgical procedure in the post-operative recovery unit. Recruited subjects will not be followed long-term.

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5.3 Device Management

There are two Precision Flow Hi-VNI devices in the PCAM equipment storage room. The surgical procedures planned for this study will be performed at PCAM. These devices will be stored according to the manufacturer's requirements and in compliance with the Penn peri-op policies for storage of standard anesthesia and peri-op equipment. No special storage or processing will be required when these devices are used for our research study. The devices will be used by fully-trained personnel, as the PI, co-Is, and research staff, as well as anesthesia support staff, had an in-service with the manufacturer's representative to learn how to use these devices. Disposable parts needed for the devices will be discarded after one use. All disposables will be provided by the manufacturer, Vapotherm, Inc.

5.4 Subject Withdrawal

All study subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the PI and co-Is if it is determined that they are not good candidates for Hi-VNI use immediately prior to surgical procedure or during the surgical procedure. This decision will be made based on a joint discussion between the airway surgeon and the anesthesiologist.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who choose to withdraw from the study or will be withdrawn from the study at the discretion of the PI or co-I will not require any additional follow-up data collection for this study.

5.5 Efficacy Evaluation

The ability of the Hi-VNI device to provide adequate oxygenation has already been demonstrated based on existing literature and a small number of cases performed at our institution. However, further evaluation of the efficacy for this oxygenation technique during upper airway surgery is one of the primary objectives for this study. All information captured during this study will contribute to our present knowledge about the ideal clinical cases and patient characteristics when Hi-VNI should be selected for upper airway procedures performed under general anesthesia.

6 Statistical Plan

6.1 Sample Size and Power Determination

The subjects will be recruited prospectively based on the eligibility criteria for this study. The investigators anticipate that 100 subjects will be recruited for this study between January 2020 and January 2021. This sample size is determined based on the previously noted caseload for our practice and the fact that this study duration will be limited to one year only. No comparison or control group will be used for this study. The calculation of statistical power will not be required. Patel et al showed that a rate of rise in pCO2 was 0.15 kPa/min with Hi-VNI oxygenation while measuring end tidal CO2 transcutaneously, which translates into 1.125 mmHg/min.[3] Another study by Gustaffson et al cited average apnea duration during elective

laryngeal surgery of 22.5±4.5 min.[13] Based on these values of the rate of rise for pCO2 and the average apnea duration for elective laryngeal surgery, assuming normal data distribution, the range of TcpCO2 change for procedure length within one standard deviation of the mean value (22.5 min) will be [20.25; 30.38].

Using a normal end-tidal CO2 value of 37.5 mmHg and adding this value to the limits of the range of change in TcpCO2 listed above will give us a range of the values for TcpCO2 at the end of the procedure assuming the average duration of the procedure is 22.5±4.5 min. This range of the TcpCO2 at the end of the procedure would be [57.75; 67.88]. Our cutoff of TcpCO2 minus the baseline gradient between TcpCO2 and end-tidal CO2 > 55 mmHg is when the mode of oxygenation will be changed from Hi-VNI to an alternate method (endotracheal intubation or HFJV). The baseline gradient will be measured as the TcpCO2 minus the end-tidal CO2 during routine pre-oxygenation with a facemask. Based on the normal distribution assumption, one can deduce that only procedures with the duration one standard deviation away from the mean duration value of 22.5 min will not reach this level of TcpCO2. In other words, approximately 16% of patients will not require alternate means of ventilation (population which falls to the left of the line through a value of (22.5-4.5) on the normal distribution curve or 15.85%). Based on the author's prior experience and operative volume, there are 2-3 elective cases per week performed by the PIs that may qualify based on the inclusion/exclusion criteria to be included in the study. If 3 cases per week is used will equal to 144 qualified cases per year. For the confidence interval of 95% and the margin of error of 5% with the rate of 16%, the calculated sample size will equal to 86 individuals who might have a good chance of having their procedure completed with Hi-VNI without a need to switch to alternate mode of oxygenation. To account for the fact that some patients may not consent to be in the study or may require alternate means of oxygenation after Hi-VNI is used for other reasons, we added 14 patients to the sample size. This would lead to an estimated sample size of 100 individuals.

6.2 Statistical Methods

Descriptive statistics will be used to characterize the data distribution with normally distributed data presented as means and standard deviation, otherwise median and interquartile range will be used. Proportions will be presented in numbers and percentages. All data analyses will be performed using a statistical tool (SPSS, version 15.0, SPSS). Mann-Whitney U test or Student's t-test and Kruskal-Wallis or ANOVA test will be used depending on the data distribution and the number of variables. All statistical analyses will use a $p<0.05$ as statistically significant. Any additional statistical analyses will be determined during secondary data analysis with help from a statistician.

6.3 Control of Bias and Confounding

This is an interventional study that will involve recruitment of subjects who are scheduled to undergo an upper airway surgery and are good candidates for use of Hi-VNI during their procedure. The investigators for this study expect some degree of bias during the subject recruitment phase, but this selection bias will help exclude patients who will not tolerate use of Hi-VNI for oxygenation during surgery due to their co-morbidities. Please see Section 4.4 for exclusion criteria defined for this study.

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6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

The primary outcomes of interest will be analyzed based on the data distribution with a goal of determining the averages and the standard deviations within the dataset.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event/Adverse Device Effect

An adverse event (AE)/adverse device effect (ADE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- Is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious AE is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

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Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3 Recording of Adverse Events

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.4 Relationship of AE to Study

The PI will determine the relationship of each adverse event to the study procedures. Relationship will be classified as definitely related, probably related, possibly related, or not related.

7.5 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days.

7.5.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

7.5.2 Data and Safety Monitoring Plan

The PI and the co-Is for this study will be responsible for data and safety monitoring. No formal data safety monitoring committee will be designated for this study since the PI and the sub-Is will closely monitor data safety for this study.

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8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

8.2 Data Collection and Management

The primary source of data collection for this study will be the current electronic medical record (EMR) system used at the University of Pennsylvania Health System (UPHS) and intra-operative/post-operative findings and observations recorded by the study personnel. During the selection of potential study participants, the electronic medical records will be reviewed by the PI/Co-Is, who will confirm eligibility based on the inclusion and exclusion criteria. If the case meets eligibility, the research team will proceed with informed consent either prior to or on the day of the scheduled surgical procedure.

Qualified patients will be assigned a unique study identification number (UID). Data will be abstracted electronically in a comma separated variable format for a statistical software package. The databases will be maintained on an institutionally secured and managed network drive. Only members of this research study team will have access to the data. Birth date will only be used to calculate an exact age in years and months. Upon completion of data collection, the age will replace the birth date. A master data sheet will include the relevant personal health information (PHI) for the study with the matching UID numbers. A separate data sheet used for statistical analyses will have only the UID numbers with de-identified information.

8.3 Records Retention

The electronic data as well as paper and digital records collected during this study will be destroyed within five years following publishing.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI and sub-Is will be responsible for ensuring the ongoing quality and integrity of the research study.

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9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents. The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Ethical Considerations

All study team members have experience/training in clinical research and have completed their CITI human subjects training. All study team members will be asked to document their role on the study delegation log. Ongoing training will take place as needed. The investigators will maintain open communication with study staff and IRB, and will submit protocol changes to IRB for approval prior to implementing them.

10.1 Risks

All subjects included in this study will be informed about potential risks associated with the use of the Hi-VNI device during surgery based on the previously published studies and the safety information reported by the Hi-VNI device manufacturer. These risks include nasal discomfort and/or rhinorrhea. To our knowledge, no other risks have been previously directly linked to Hi-VNI use. These side effects of Hi-VNI use could be related to dry nasal mucosa after use of high-flow nasal insufflation, and will prescribe nasal saline sprays and recommend Tylenol or other mild over the counter analgesics in cases when patients report symptoms of nasal pain and/or rhinorrhea.

To minimize the risk of inadequate oxygenation and other complications, careful continuous monitoring will be maintained throughout the case. All patients will receive preoxygenation with a bag-mask to ensure that mask ventilation can be performed successfully during the case if needed and to determine the baseline gradient between end-tidal CO2 and TcpCO2. If mask ventilation during the induction phase is unsuccessful, the anesthesia team will intubate the patient or HFJV will be initiated after exposure of the glottis by the airway surgeon, and the patient will be withdrawn from the study.

The Hi-VNI device will be used during the surgical procedure with continuous monitoring by anesthesia team. If at any point the SpO2 drops below 90% or the value of TcpCO2 minus the baseline gradient rises above 55 mmHg, the airway surgeon and the anesthesiologist will stop the procedure and will switch to an alternate means of oxygenation immediately by placing an HFJV cannula or a small sized endotracheal tube through the laryngoscope into the glottis/trachea (a step performed in the beginning of the case if HFJV or endotracheal intubation are selected as primary methods of oxygenation during the case). Continuous monitoring in the OR will help us avoid TcpCO2 minus the baseline gradient levels above 55 mmHg (levels of TcpCO2 not previously correlated clinically with PaCO2). As soon as this threshold value is reached, the surgeon will place an endotracheal tube through the

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laryngoscope. A total of 5 breaths will be administered via the endotracheal tube to determine the ETCO2 reading. If the ETCO2 reading is above 60 mmHg, the patient will be ventilated via the endotracheal tube. In other words, continuous monitoring will ensure that clinically significant hypoxia or hypercarbia (defined as SpO2 level below 90% or ETCO2 levels above 60 mmHg) that could eventually lead to adverse events if not promptly corrected will always be avoided by immediate switch to alternate means of oxygenation. HFJV equipment, a small sized endotracheal tube, and all standard operating room airway and resuscitation equipment will be available as is the current standard during each case to allow for safe use of Hi-VNI and to prepare for the cases in which alternate means of oxygenation may be required.

All precautions will be taken to prevent vital sign changes that affect the accuracy of TcpCO2 measurements including changes in blood pressure, abnormal heart rhythm or body temperature changes. Warming blankets will be used to avoid hypothermia. If a patient develops a transient arrhythmia or hypotension requiring vasopressor administration during the procedure, which can cause erroneous SpO2 and inaccurate TcpCO2, the patient will be intubated and the procedure will be completed with oxygenation/ventilation via the endotracheal tube. If the procedure cannot be performed with the endotracheal tube in place, the procedure will be aborted. If the arrhythmia persists, or if the nature of the arrhythmia is considered to warrant procedure termination, the procedure will be aborted. Additionally, if use of Hi-VNI support extends beyond 20 minutes, a blood sample will be drawn to evaluate CO2 level (PaCO2 or PvCO2). If the blood sample collection cannot be done, the patient will be intubated and ETCO2 will be measured.

If at any point during the procedure, a bleeding is encountered that requires cautery, the team will switch to an endotracheal tube to prevent aspiration of blood into the airway and to allow for appropriate hemostasis with use of cautery. If at any point during the procedure, it will become evident that the laser use is necessary, the team will switch to an alternate means of oxygenation. Standard practices currently in place to avoid airway fire will be used if the case demands use of electrocautery or laser. These practices will be implemented immediately once it becomes evident that either laser or electrocautery will be used. If laser or electrocautery will be used to control the bleeding during the case, following an endotracheal intubation, appropriate washout of residual oxygen will take place per routine protocol, and the laser or cautery will not be used until FiO2 levels reach the values below 21%. All standard fire precautions will be used and the oropharynx will be suctioned to remove any potential residual oxygen excess. All cases will be screened prior to enrollment into the study to avoid inclusion of the cases with high risk of large-volume bleeding requiring cautery or with a need for laser use during the procedure.

Any upper airway procedure we perform begins with direct laryngoscopy and the exposure of the glottic airway with a laryngoscope. With the exposed view of the vocal cords/glottic opening, the exchange step of endotracheal intubation or placement of the HFJV cannula takes a few seconds. The surgical and anesthesia staff assigned to these cases are familiar with the exchange from one mode of oxygenation to another since this is commonly performed for these cases. After performing a portion or the entire case with HFJV, the team then elect to intubate the patient for the final steps of the surgical case or for emergence from

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anesthesia. In cases where HVNI is used the surgeon and anesthesiologist team will then decide if the patient will continue to receive oxygenation through the nasal cannula, get mask ventilated or get intubated. Investigators for this study do not anticipate any additional risks to the patient or significant additional time needed to complete these procedures during this study, even in the cases where use of Hi-VNI alone is insufficient.

Patients who are not candidates for Hi-VNI use will be excluded from this study. These patients include those with underlying medical conditions in which brief periods of hypoxemia or hypercarbia are not well-tolerated, such as pregnant patients, patients with coronary artery disease or carotid/vertebral artery stenosis, patients with severe heart failure or implanted ICD, patients with extremely low or extremely high BMI or patients with baseline hypoxia and oxygen requirement at home. Additionally, patients in whom use of high-flow oxygenation is contraindicated, such as patients with increased intracranial pressure or history of skull base surgery, will be excluded. Patients at high risk for aspiration and patients scheduled for emergent or urgent interventions will also be excluded.

10.2 Benefits

The potential direct benefits to the subjects who will consent to participate in this study are a chance of shorter surgical case duration, potential avoidance of intubation, and lower risk of barotrauma and airway trauma if Hi-VNI is used without a need for intubation or HVJV use during the procedure. This study also offers indirect benefits to the society and the future patients by attempting to further evaluate the efficacy of the Hi-VNI as a primary or adjunct oxygenation technique during upper airway surgery. This study will not change labeling of the Hi-VNI Precision Flow device by the Vapotherm and is not intended to change marketing claims of the manufacturer.

10.3 Risk Benefit Assessment

The Risk Benefit Assessment will be done for each individual subject before proceeding with the enrollment to ensure that use of Hi-VNI during upper airway surgery does not predispose the potential subject to any foreseeable harm or risk of complications. This assessment will involve a joint discussion between the airway surgeon (the PI) and the anesthesiologist (the sub-Is).

10.4 Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a combined consent/HIPAA authorization form (attached) describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject undergoes any study procedure. The subject and the investigator-designated research professional obtaining the consent will sign the consent form. Subjects will be consented by the study Principal Investigator, or appropriate designee, in a private room where their discussions are unlikely to be overheard and their privacy is priority. Potential subjects will review the consent form in

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detail with the person designated to consent and will have the ability to take the consent home for further review.

11 Study Finances

11.1 Funding Source

None. The manufacturer of the device, Hi-VNI Precision Flow, will provide the devices needed for this study (Hi-VNI Precision Flow and SenTec monitor) and the disposables needed for their use. No additional funding will be provided.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

None

12 Publication Plan

The Principal Investigator intends to present the results at a national conference and publish the study results in a peer-reviewed medical journal.

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