# TMU-Joint Institutional Review Board

# Protocol Title: An Investigation of Optimal Anesthesia for Morbidly Obese Patients Undergoing Bariatric Surgery: A randomized controlled trial

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**List of abbreviations:**

BIS: bispectral index

BMI: body mass index

CPAP: continuous positive airway pressure

ERAS: Enhanced Recovery After Surgery

EEG: electroencephalography

$FiO_2$: fraction of inspired oxygen

HFNC: high-flow nasal cannula

IRB: Institutional Review Board

LSG: laparoscopic sleeve gastrectomy

NRS: Numeric rating scale

OSA: obstructive sleep apnea

PEEP: positive end-expiratory pressure

$PaO_2$: arterial partial pressure of oxygen

$SpO_2$: peripheral oxygen saturation

## Introduction

Obese patients have a higher risk of anesthesia compared to the non-obese, including difficult intubation, rapid desaturation, difficult vascular access, and delayed recovery from anesthesia. This study aims to investigate the optimal anesthesia strategy for morbidly obese patients undergoing bariatric surgery in airway management, preoxygenation, arterial cannulation, and type of volatile anesthetic with M-Entropy guidance. The investigators will conduct a two-year clinical trial using permuted block randomization to evaluate multiple outcomes in patients undergoing laparoscopic sleeve gastrectomy (LSG) at Shuang Ho Hospital, Taipei Medical University. Particularly, the investigators will explore the role of ultrasound, an easily accessible modality for anesthesiologists, in examining upper airway anatomy and guiding arterial cannulation. The investigators will also assess the effectiveness of high-flow nasal cannula as a preoxygenation tool in preventing desaturation.

The investigators will conduct a clinical trial using permuted block randomization and conforming to the CONSORT Statement to investigate multiple clinical outcomes in obese patients undergoing LSG at Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan. Three randomizations will be conducted, including radial artery catheterization using ultrasound guidance or blind palpitation, preoxygenation using high-flow nasal cannula (HFNC) or conventional facemask, and volatile anesthesia with desflurane or sevoflurane with or without M-Entropy guidance.

## Background

Obesity is one of the major epidemics of the twenty-first century.[1] The worldwide prevalence of overweight and obesity has doubled since 1980, and almost a third of the global population is now classified as overweight or obese.[1] In Taiwan, the prevalence of mild-to-moderate obesity (body mass index (BMI) range, 27 – 35 $kg/m^2$) has increased nearly twofold from 1993 to 2014 and over threefold for morbid obesity (BMI range, > 35 $kg/m^2$).[2] Nowadays, morbid obesity has affected more than 5 million people on the island.[2] In addition to cardiovascular and metabolic disorders, obese patients have an increased risk for various types of diseases, including liver and gallbladder diseases, gastroenterological cancers, endometrial cancers, and osteoarthritis, which also increases the number of obese patients for surgical procedures and anesthesia.[3,4]

Bariatric surgery is recommended at a BMI > 40 $kg/m^2$ or BMI > 30 $kg/m^2$ when obesity-related comorbidities (e.g. hypertension, diabetes, and dyslipidemia) are expected to improve with weight loss after surgical intervention.[5] In clinical trials, long-term mortality risk is significantly lowered in surgically treated groups compared to medically managed patients, particularly in deaths from diabetes, heart disease, and cancer.[6] Besides, compared to medication therapy alone, bariatric surgery plus intensive medical therapy is more effective in decreasing hyperglycemia among diabetic and obese patients.[7] Due to the health benefit of bariatric surgery and the advance in laparoscopic techniques, bariatric surgery has had almost tenfold growth worldwide in the past two decades, increasing from 40,000 bariatric procedures in 1997 to nearly 400,000 in 2016.[8,9]

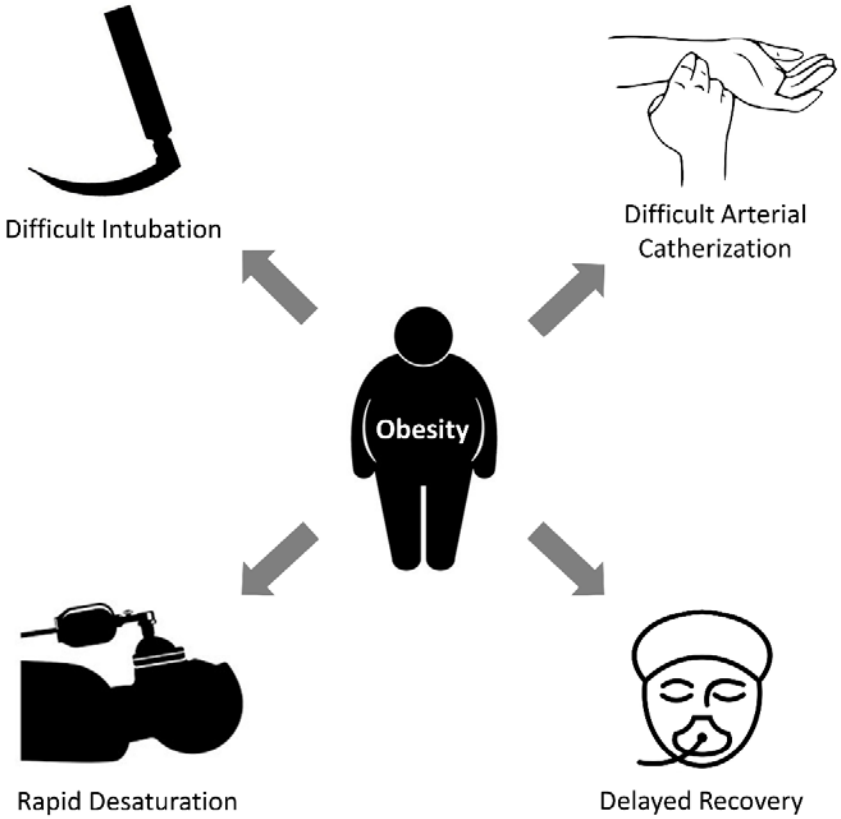


**Figure 1: Obese Patient as an Anesthesia Challenge**

***Obesity Patient as a Challenge in Anesthetic Management***

Obese patients represent an evident challenge in anesthetic management due to their higher risks of difficult intubation and ventilation, impaired pulmonary functions, difficult vascular access, and delayed recovery from anesthesia.[10] (Figure 1) Study has showed the risk of difficult tracheal intubation is higher in obese patients with a three times higher risk compared to the nonobese.[11] Besides, obese patients have multiple respiratory abnormalities, including reduced vital capacity, inspiratory capacity, expiratory reserve volume, functional residual capacity, and lower lung compliance.[12] Obesity is also the greatest risk factor for obstructive sleep apnea (OSA)[13], which predisposes obese patients to higher risks of difficult ventilation and rapid oxygen desaturation during induction of general anesthesia.[14] Study has showed the nonhypoxic apnea time of peripheral oxygen saturation ($SpO_2$) decreasing to 90% after facemask preoxygenation is less than 3 minutes in obese patients compared to 6 minutes in patients having a normal BMI.[15] In addition to respiratory complications in anesthesia, morbidly obese patients are prone to have a difficult arterial puncture because of their excessive subcutaneous tissue and higher risk of vascular complication after arterial puncture.[16]

Morbidly obese patients are susceptible to low emergence from anesthesia due to delayed release of volatile agent from excessive adipose tissue.[17] They have an increased risk of lingering respiratory depression effects of anesthetic drugs. However, the current Enhanced Recovery After Surgery (ERAS) protocol does not recommend specific anesthetic agents for bariatric surgery due to mixed results of available studies.[18] Some studies showed desflurane has

consistent and rapid recovery profile compared to sevoflurane and propofol.[19-21] Conversely, other studies reported that the difference in immediate recovery between desflurane and sevoflurane is clinically non-significant.[22] Moreover, although electroencephalography (EEG)-based monitoring of anesthesia depth is widely used and effective in maintaining the optimal range of anesthesia depth in total intravenous anesthesia, there is spare evidence regarding the role of EEG-based monitoring in volatile general anesthesia for obese patients.[23]

***Difficult Laryngoscopy Intubation***

Obese patients have a high risk of difficult laryngoscopy due to their short, thick neck, large tongue, and significant redundant pharyngeal soft tissue.[11] However, till now there is no established predictor for difficult intubation in obese patients. One study reported a correlation between oropharyngeal Mallampati score and BMI as predictors of difficult laryngoscopy.[24] However, another study showed BMI was not associated with difficult intubation in obese patients.[25] Although Mallampati score may predict potential intubation difficulties, intubation by direct laryngoscopy was successful in 99% patients.[25] Other investigators demonstrated that Mallampati score had low specificity (62%) and low positive predictive values (29%) for difficult intubation.[26] Interestingly, an abundance of pretracheal soft tissue measured ultrasonically and neck circumferences may predict difficult laryngoscopy.[27,28]

***Difficult Arterial Cannulation***

*The common cardiovascular comorbidities present in obese patients frequently necessitate* continuous arterial pressure monitoring in surgery.[29] However, it is more difficult for clinicians to perform an arterial catheterization in obese patients due to their excessive subcutaneous tissue. Besides, obese patients tend to have a higher risk of vascular complication after arterial catheterizations.[16] Therefore, strategy to increase the success rate of arterial cannulation and reduce potential vascular complications becomes an important issue for obese surgical patients.

Ultrasound guidance has emerged as a useful tool for central vein catheterization with the advantages of higher success rate, patient safety, and cost-effectiveness.[30] For radial artery catheterization, ultrasound guidance is also an effective and safe technique, especially in pediatric population.[31-33] For resident physicians, ultrasound achieved significantly faster placement of the arterial lines, fewer attempts, and fewer catheters used.[34] However, the effectiveness and safety of ultrasound-guided arterial catheterization have not been investigated in obese patients. Besides, ultrasound offers the most accurate measurement for thickness of subcutaneous adipose tissue layers.[35] The distance from skin surface to commonly-catheterized arteries (e.g. radial artery, brachial artery, and femoral artery) has not been explored in obese patients.

***Preoxygenation Strategy to Prevent Desaturation***

Multiple strategies to prolong nonhypoxic apnea time in the induction of anesthesia have been investigated, including use of CPAP during preoxygenation, facemask application of positive end-expiratory pressure (PEEP), and mechanical ventilation following induction of anesthesia.[36-38] Application of 10 cm $H_2O$ CPAP during preoxygenation achieved a higher arterial partial pressure of oxygen ($PaO_2$) after intubation and reduced the amount of atelectasis.[36] Similarly, use of CPAP 10 cm $H_2O$ with post-induction mechanically ventilation with PEEP 10 cm $H_2O$ for 5 min prolonged the nonhypoxic apnea time from 127 seconds to 188 seconds.[37] However,

preoxygenation of 7.5 cm $H_2O$ CPAP for 3 minutes did not increase the nonhypoxic apnea time to an $SpO_2$ of 90% for obese patients.[38] Preoxygenation using 25 degrees head-up position increased the nonhypoxic apnea time to an $SpO_2$ of 92% and also achieved 23% higher oxygen tensions.[39]

Recently, HFNC is widely used in patients receiving sedative procedures. HFNC is able to deliver up to 60 L/min gas flow with a fraction of inspired oxygen ($FiO_2$) 100%.[40] It may also produce a low level of positive airway pressure and improve patient comfort compared to facemask ventilation.[41] The effectiveness of HFNC in preventing arterial oxygen desaturation of obese patients has been compared with standard nasal cannula or facemask ventilation in various settings.[42-45] In propofol sedation for colonoscopy, HFNC was not better than standard nasal cannula for prevention of arterial oxygen desaturation.[42] In induction of general anesthesia, HFNC prolonged the nonhypoxic apnea time by 76 seconds (40%) and enhanced minimum $SpO_2$ in morbidly obese patients.[43] Another study recently showed the use of HFNC at the time of extubation reduced postoperative hypoxemia in obese patients after bariatric surgery compared to receive conventional oxygen therapy.[44] However, a randomized trial reported that preoxygenation with HFNC offered lower end-tidal oxygen concentration after intubation and a higher risk of desaturation < 95% in obese patients.[45] The available evidence is conflicting regarding the effectiveness of HFNC for prevention of perioperative desaturation, and the most optimal strategy of preoxygenation in general anesthesia has not been clearly clarified for obese patients.

***Delayed Recovery from Anesthesia***

Recovery from anesthesia might be compromised in obese patients due to delayed release of volatile anesthetics from excessive fat tissue.[17] However, evidence regarding optimal anesthesia strategy to enhance obese patients' recovery is still insufficient and conflicting.[18] Randomized trial has showed that anesthetic maintenance using desflurane achieves more rapid postoperative immediate and intermediate recoveries than propofol or isoflurane anesthesia.[19] Similarly, another study reported obese patients receiving bispectral index(BIS)-guided desflurane anesthesia had faster immediate recovery, eye opening, extubation, airway maintenance, and orientation compared to sevoflurane anesthesia.[20] However, other investigators claimed that the differences in immediate recovery between desflurane and sevoflurane are not clinically significant.[22,46]

Meta-analysis has showed that BIS-guided anesthesia may enhance early recovery times in patients undergoing surgery under general anesthesia compared to clinical signs.[47] However, few studies have investigated whether anesthesia with EEG-based monitoring of anesthesia depth improves the postoperative recovery in obese patients. Ibraheim and colleagues reported that patients receiving BIS-guided sevoflurane anesthesia had significantly faster awakening and shorter extubation time, and lower sevoflurane consumption and cost compared to the control group.[48] However, this study had a small patient sample and did not evaluate other volatile anesthetics, such as desflurane anesthesia.[48]

**Eligible Criteria**

Adult obese patients (BMI ≥ 30 $kg/m^2$) undergoing LSG at Shuang Ho Hospital, Taipei Medical University will be included. Exclusion criteria will be severe cardiopulmonary disease, psychiatric disorder, history of head and neck surgery or radiation therapy, cervical spine injury,

renal insufficiency (estimated creatinine clearance < 60 ml/min), $SpO_2$ < 90% in room air, hemodynamic instability, preexisting arterial catheterization during the same visit within 7 days, and patient refusal.

**Objectives of Study**

The main objective of this study is to investigate the optimal anesthesia strategy in the airway evaluation, preoxygenation, arterial cannulation, and choice of volatile anesthetics in obese patients undergoing bariatric surgery, as the followed:

1. To explore potential predictors for difficult intubation using ultrasound evaluation of upper airway anatomy and tongue base
2. To evaluate the safety and effectiveness of ultrasound-guided radial artery catheterization compared to traditional blind-palpation method
3. To compare the effectiveness of high-flow nasal cannula and facemask in the preoxygenation of general anesthesia
4. To compare the effect of different volatile anesthetics and M-Entropy guidance on the postoperative recovery in obese patients.

**Study Protocol**

The investigators will conduct a clinical trial using permuted block randomization and conforming to the CONSORT Statement[49,50] to investigate multiple clinical outcomes in obese patients undergoing LSG at Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan. Three randomizations will be conducted, including radial artery catheterization using ultrasound guidance or blind palpitation, preoxygenation using HFNC or conventional facemask, and volatile anesthesia with desflurane or sevoflurane with or without M-Entropy guidance. A computer-generated list of randomizations (Research Randomizer, www.randomizer.org) will be used for these group allocations.

The flow diagram for research conduction is shown in Figure 2. Before surgery, every participant will undergo echocardiography to rule out severe cardiopulmonary disease (LVEF < 40% or moderate-to-severe pulmonary hypertension or confirmed diagnosis of coronary artery disease)

**Substudy 1. Exploring potential risk factors of difficult intubation using ultrasound: A prospective single-blind cohort study**

Before surgery, all enrolled patients will be examined for appearance features regarding difficult airway, including interincisor distance (< 3 cm or not)[51], mentohyoid distance, thyromental distance (< 6.5 cm or not)[52], neck movement (< 80 degrees or not)[53], neck circumference measured at the thyroid cartilage (> 43 cm or not)[28], modified Mallampati score[54], upper lip bite test[55], and mandibular prognathism test[56]. Besides, ultrasound will be used to assess upper airway anatomy, including pretracheal soft tissue depth[27] and height and width of tongue base[57]. Regarding pretracheal soft tissue depth, the distance from the skin to the anterior aspect of the trachea will be measured at three levels: vocal cords, thyroid isthmus, and suprasternal notch.[27] The amount of soft tissue at each zone is calculated by averaging the amounts of soft tissue in millimeters obtained in the central axis of the neck and 15 millimeters to the left and right of the central axis.

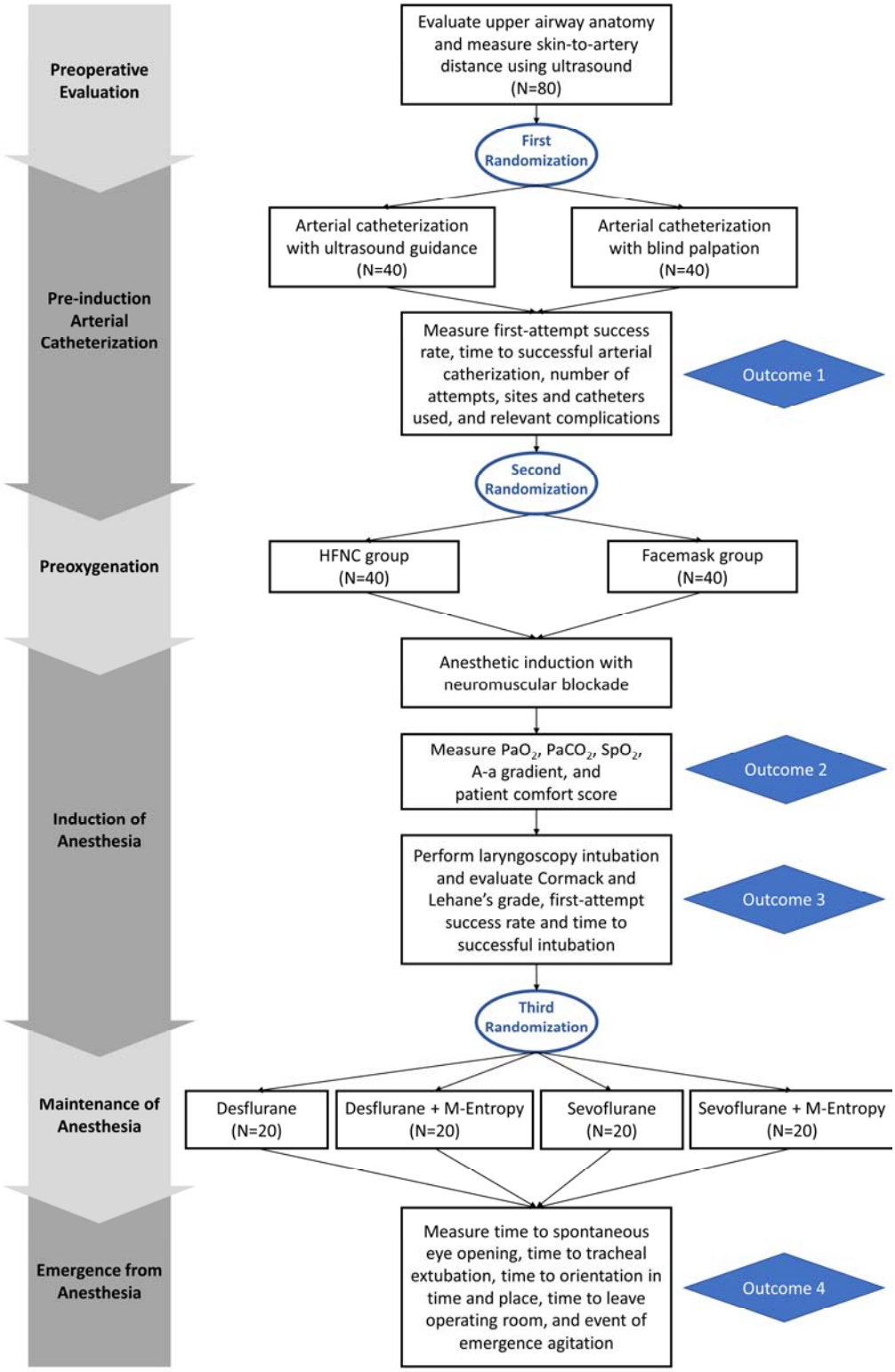


**Figure 2: Flow diagram for research conduction**

Moreover, the increased tongue volume and deposition of fat at the base of tongue in obese people has been shown to be highly associated with risk of obstructive sleep apnea.[58] To measure the anatomy of tongue base, with the patient in a seated position, the convex transducer in the frequencies 1.5 to 5.0 MHz (GE C1-5-RS, GE Healthcare, Chicago, IL, USA) of a portable ultrasound device (LOGIQ™, GE Healthcare, Chicago, IL, USA) will be introduced to the skin of the neck in the submental region coronally, immediately cephalad to the body of the hyoid bone, and then in the area between the hyoid bone and the symphysis of the mandible. The patients will be instructed to avoid tongue movements, swallowing, or talking.[57] Maximal width of tongue base, tongue base height, and maximal height of mid-tongue will be measured.

The same anesthesiologist will perform all ultrasound measurements before surgery. Upon arrival at operating room, patients will be initially placed in a ramped position and then moved into a reverse Trendelenburg position to achieve a 30-degree incline of the thorax before preoxygenation. After induction of anesthesia, another anesthesiologist, blinded to all preoperative evaluation, will perform all laryngoscopies in this study. The laryngoscopy intubation will be performed using a size-3 or -4 Macintosh (Rüsch Inc., Duluth, GA, USA) blade and a styleted endotracheal tube. The laryngoscopic view will be graded according to Cormack and Lehane's classification with external laryngeal pressure applied.[59] Laryngoscopy views graded as III or IV are defined as difficult. In case of failed direct laryngoscopy despite external laryngeal manipulation in the first attempt, video-assisted laryngoscope GlideScope® (Verathon Medical, Bothell, WA, USA) will be used as an intubation rescue technique. The video-assisted laryngoscope will be kept on standby at the operating room before induction. The correct placement of the endotracheal tube will be confirmed by capnography. Primary outcome is occurrence of difficult laryngoscopy. Secondary outcomes are first-attempt success rate and time to successful intubation.

**Substudy 2. Radial artery catheterization using ultrasound guidance or blind palpation: An open-label randomized controlled trial**

Before surgery, the investigators will use a portable ultrasound device (LOGIQ™, GE Healthcare, Chicago, IL, USA) to measure the skin-to-artery distance of common sites of arterial cannulation of all enrolled patients, including radial artery, brachial artery, and dorsalis pedis artery. Patients will be randomized in a ratio of 1:1 into ultrasound group (N=40) or palpation group (N=40). Radial artery cannulation will be performed using a radial artery catheterization kit (Arrow International Inc, Reading, PA, USA). For all patients, the wrist will be extended and taped to a board to maintain wrist extension, and the skin near the puncture site will be cleaned with chlorhexidine according to standard protocol. Allen test will be used to assess the vascular patency of the hand before cannulation of the radial artery.[60] All patients will receive local skin anesthesia at the anticipated puncture site. All radial artery catheterizations will be performed by trained year 1 or 2 anesthesiology residents with similar levels of experience in both blind-palpation and ultrasound-guided radial arterial catheterization. All residents have performed at least 5 blind-palpation and 5 ultrasound-guided radial arterial catheterizations prior to the study.

In the ultrasound group, a linear vascular probe in the frequencies 5 to 13 MHz (GE 12L-RS, GE Healthcare, Chicago, IL, USA) of portable ultrasound device (LOGIQ™, GE Healthcare, Chicago, IL, USA) will be applied to the skin to localize the radial artery and a 20-gauge catheter will be inserted distal to the transducer and directed according to the ultrasound image. Start time is defined as the time when the ultrasound probe is placed on the wrist. In the palpation group,

the radial artery will be identified by palpation, and the cannula will be directed by continuous or intermittent palpation of arterial pulsation. The attending anesthesiologist will supervise the resident and act as the second operator if needed. An attempt is defined as a new penetration of the skin with the needle, followed by an unlimited number of subcutaneous needle redirections. Clinical judgment by the supervising anesthesiologist is used to determine the time allowed for an attempt, number of attempts allowed, and changes to a new site. The attending anesthesiologist will take over arterial cannulation if residents perform for more than 3 times or > 15 minutes. The start time is defined when the operator's finger is initially placed on the patient's wrist. The end point for both methods is when the arterial catheter is successful placed. Primary outcome is first-attempt success rate, and secondary outcomes comprise time to successful arterial catheterization, number of attempts, sites and catheters used. Complications related to arterial cannulation will also be recorded, including pain, hematoma formation, and arterial vasospasm or occlusion.

**Substudy 3. Comparing the effectiveness of preoxygenation between HFNC and facemask: A single-blind randomized controlled trial**

Patients will be randomized in an allocation ratio of 1:1 into HFNC group (N=40) or facemask group (N=40). Preoxygenation will be performed according to the randomization group for a 5-minute duration. In the HFNC group, preoxygenation will be performed using HFNC (Optiflow™, Fisher & Paykel Healthcare, Auckland, NZ), nasal prongs set at 30 L/min flow of heated and humidified 100% oxygen. In the facemask group, patients will breath spontaneously with an anesthetic facemask and 100% oxygen 15 L/min.[61] Gas flow for HFNC or facemask can be adjusted depending on patients' tolerance. After preoxygenation, general anesthesia will be induced with propofol 1.5 – 2.0 mg/kg ideal body weight, alfentanil 8 – 10 μg/kg total body weight, and rocuronium 0.8 – 1.0 mg/kg ideal body weight. Rapid sequence intubation will be performed in all patients. During laryngoscopy intubation, HFNC will be left in place with the nasal flow escalated to 50 L/min of 100% oxygen in order to achieve apneic oxygenation. In the facemask group, the facemask will be removed when apnea occurs. After tracheal intubation, correct placement of the endotracheal tube will be confirmed by capnography and the nasal prongs of the HFNC group will be removed. If desaturation ($SpO2 < 92\%$) occurs, patients will be then administered 100% $O_2$, and the recruitment maneuver (peak airway pressure 40 cm $H_2O$ for 10 seconds) will be applied until $SpO_2$ restores to baseline values. Primary outcome is PaO2 after preoxygenation. Secondary outcomes are SpO2 before preoxygenation, after preoxygenation, and after intubation, desaturation event ($SpO2 < 92\%$), the lowest SpO2 during intubation, PaO2 before preoxygenation, and PaCO2 before and after preoxygenation, alveolar-arterial oxygen gradient (A-a gradient)[62], and patient comfort levels. All the outcomes will be measured by a nursing anesthetist, blinded to group allocation. Arterial line will be placed before induction. Arterial blood gas will be measured twice: first, before the preoxygenation in room air and, second, just after the 5-minute preoxygenation. Comfort levels of the HFNC and standard facemask will be assessed using a 10-point Likert scale, and patients will be asked which of the two devices they preferred regarding comfort before referral to ward.

**Substudy 4. The effect of type of volatile anesthetics and M-Entropy guidance of anesthesia depth on postoperative recovery: A double-blind randomized controlled trial**

Patients will be randomized by a computer-generated list into one of the four groups, desflurane with usual care (N=20), desflurane with M-Entropy guidance (N=20), sevoflurane with usual care (N=20), and sevoflurane with M-Entropy guidance (N=20). At the operating room, a M-Entropy™ sensor and S/5™ module (GE Healthcare, Helsinki, Finland) will be applied to all patients' forehead before induction of anesthesia according to the manufacturer's recommendations. This will be connected to a M-Entropy Monitor that will be concealed from the patients and operators.

In the M-Entropy group, dosage of volatile anesthetics will be adjusted to achieve the Response and State Entropy value between 40 and 60 from the start of anesthesia to the end of surgery. In the usual care group, dosage of volatile anesthetics will be titrated according to clinical judgment. This will be to maintain arterial pressure within 20% range of the baseline and the heart rate within the range 50 to 100 beats/min. In case of signs of inadequate anesthesia (e.g. movement, cough and swallowing), anesthetic dose will be increased. M-Entropy monitoring will be continued in the usual care group, but the Entropy number and EEG waveform will be concealed from the anesthetist in charge. Entropy values, hemodynamic, and expiratory gas data will be recorded in 5-min intervals. In all patients, cessation of general anesthesia will be timed to facilitate early awakening after wound closure. All patients will be decurarized from rocuronium-induced neuromuscular blockade with sugammadex dosed at 2 mg/kg ideal body weight + 40%.[63] Primary outcome is time to spontaneous eye opening. Secondary outcomes include time to tracheal extubation, time to orientation in time and place, and time to leave operating room, event of emergence agitation. The Richmond Agitation-Sedation Scale (RASS) will be used to evaluate the level of agitation and sedation promptly after extubation.[64] For patients who are transferred to the intensive care unit for postoperative mechanical ventilation, the investigators will record the time to extubation.

**Statistical Analysis Plan**

The distributions of baseline patient characteristics and outcome variables will be compared between two groups using chi-square tests or Fisher's exact test for categorical variables and either t tests or Wilcoxon rank sum tests for continuous variables, as appropriate. For four-group comparisons, either ANOVA tests or Kruskal-Wallis tests will be used for continuous variables, as appropriate. A Bonferroni correction to the significance criterion for multiple comparisons is applied where appropriate. For time to event data, Kaplan-Meier method and log-rank test will be applied for group comparisons. Multivariable logistic regression, simple linear regression, or Cox proportional hazards regression analyses will be used to identify potential influential factors of outcomes of interest. A two-sided significance level of 0.05 was used to define statistically significant difference. All the statistical analyses will be conducted using Statistics Analysis System (SAS), Version 9.4 (SAS Institute Inc., Cary, NC, USA).

According to prior study[37], at least 37 patients in each group of HFNC or facemask preoxygenation are needed to detect a difference of 30 seconds of nonhypoxic apnea time between the HFNC and facemask group, accepting a type I error of 5% and type II error of 20% with anticipated nonhypoxic apnea time of mean 188 ± SD 46 seconds in the facemask group.[65] Nevertheless, in order to allocate 20 patients into each group of volatile anesthesia with desflurane or sevoflurane with or without M-Entropy guidance, a total of 80 patients will be enrolled in this study.

There are about 120 patients undergoing LSG at our hospital per year. Considering the patient selection criteria and possible patient refusal, a total of 50 patients per year will be enrolled in this study. Therefore, it will take about 2 years for patient recruitment. Besides, the investigators will select all randomized subjects for analysis.

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