TMU-Joint Institutional Review Board

Protocol Title

An investigation of the impact of anesthetic guidance of depth of anesthesia and indirect cardiac output monitoring on the clinical outcomes of patients undergoing thoracic surgery: A factorial parallel randomized controlled trial

Protocol No: N202004045
Version/Date：1/2020.04.26

List of Abbreviations:

BIS: bispectral index

CO: cardiac output

CONSORT: Consolidated Standards of Reporting Trials

ERAS: Enhanced Recovery After Surgery

EEG: electroencephalography

FiO_2: fraction of inspired oxygen

GDT: goal-directed therapy

OLV: one-lung ventilation

PaO_2: arterial partial pressure of oxygen

1. Introduction

Patients undergoing thoracotomy in thoracic surgery are prone to have complications of delayed recovery from general anesthesia and perioperative instable hemodynamics due to the relatively invasive procedures and patient's underlying morbidity. Therefore, intraoperative monitoring and corresponding management are of great importance to prevent relevant complications in thoracic surgery. This study aims to investigate the clinical benefits of two intraoperative monitoring techniques in patients undergoing thoracotomy surgery, including depth of anesthesia and minimally invasive cardiac output monitoring. First, M-Entropy system will be used to measure the depth of anesthesia and be evaluated regarding the effect of spectral entropy guidance on postoperative recovery. Second, we will apply ProAQT device in guiding goal-directed hemodynamic therapy and assess its impact on occurrence of postoperative pulmonary complications and recovery. In this study, we will conduct a factorial parallel randomized controlled trial and use the method of stratified randomization to evaluate both two monitoring technologies in the same patient group. The results of this study will provide important evidence and clinical implication for precision anesthesia and enhanced recovery after surgery (ERAS) protocol in thoracic surgery.

This study aims to investigate the clinical benefits of two intraoperative monitoring techniques in patients undergoing thoracotomy surgery, including M-Entropy system and ProAQT sensor, as follows:

1) To evaluate the effect of M-Entropy guidance on the emergence from anesthesia and risk of postoperative delirium.

2) To apply ProAQT in guiding goal-directed hemodynamic therapy and assess its impact on postoperative pulmonary complications and recovery.

2. Background

Thoracic anesthesia comprises a wide variety of diagnostic and therapeutic procedures involving the lungs, airways, and hemodynamic changes. The procedure of thoracotomy inevitably causes pneumothorax, which results in multiple physiology derangements, including ventilation-perfusion mismatch and hypoxia.[1] Furthermore, one-lung ventilation (OLV) is commonly used to facilitate the visualization and surgical manipulation in video-assisted thoracotomy. However, OLV may also cause profound hemodynamic changes, including lung collapse, barotrauma and severe hypotension.[1] The hemodynamic instability may further increase the risk of inadequate depth of anesthesia and thereafter its related complications, such as intraoperative awareness, post-traumatic stress disorder and cognitive dysfunction.[2] Therefore, intraoperative monitoring and corresponding management are of great importance to prevent relevant complications in thoracic surgery.

Because of the advances in monitoring technology in recent decades, the risk of mortality and morbidity of anesthetic practices has significantly declined.[3] Among the newly-introduced technologies, electroencephalography (EEG)-based monitoring of anesthesia depth and indirect cardiac output monitoring are useful and minimally invasive in optimizing the anesthetic patients' intraoperative hypnotic, cardiac output, and intravascular volume status.[4,5] However, there is spare evidence regarding the effectiveness of the use of these two monitoring in guiding thoracic anesthesia. Accordingly, this study aims to investigate the effect of guidance of spectral

entropy and indirect cardiac output monitoring on the recovery from anesthesia and postoperative outcomes in patients undergoing thoracotomy.

Anesthesia depth monitoring using spectral entropy

Meta-analysis has showed that bispectral index (BIS)-guided anesthesia may enhance early recovery time in patients undergoing surgery with general anesthesia compared to clinical signs.[6] However, compared with BIS, M-Entropy™ system (GE Healthcare, Helsinki, Finland) is much less investigated regarding its clinical effectiveness. The use of entropy to track the anesthetic state of patients is a relatively new monitoring approach. Entropy measures the degree of disorder or the lack of synchrony or consistency in a system.[7] Entropy-based analyses have been applied to the EEG and used to construct EEG-based indices meant to indicate the depth of anesthesia.[7] Although 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 spectral entropy monitoring in volatile anesthesia regarding time to emergence from anesthesia as well as reduction in anesthetic agent use.[8] Besides, whether entropy guidance in general anesthesia protects against development of postoperative delirium remains unclear in thoracic surgery.

Indirect cardiac output monitoring in guiding intraoperative fluid and inotrope or vasopressor therapy

There are several commercial devices in monitoring cardiac output (CO) through minimal invasive techniques.[5] The major principles and techniques of CO measurement include the Fick principle, arterial waveform analysis techniques, the Doppler principle.[9] ProAQT® device (Pulsion Medical Systems, Munich, Germany) is a modular platform with intelligent visualization for real-time patient monitoring on the basis of PiCCO pulse contour algorithm.[9] ProAQT allows physiological interpretation of the patient's hemodynamic status and supports goal directed therapy in surgical patients. Regardless of the broad use of minimally invasive CO monitoring in clinical practices, the evidence for its benefits in patients' prognosis is conflicting.[9] Furthermore, it is unclear whether application of minimally invasive CO monitoring in guiding administration of intraoperative fluid, inotrope, and vasopressor improves outcomes in thoracic surgery.[10] At present, the validity of this technology as a valid guide for fluid management when the chest is open remains unclear. Strong clinical outcomes data support the use of noninvasive stroke volume monitors in patients undergoing major surgery although these studies generally do not focus on thoracic surgical procedures.[11-13]

The value of precision anesthesia in Enhanced Recovery After Surgery (ERAS)

Patients undergoing thoracotomy are prone to have complications of delayed recovery from general anesthesia and perioperative instable hemodynamics due to the relatively invasive procedures and patient's underlying morbidity.[11,12,14,15] Current recommendations from the ERAS Society and the European Society of Thoracic Surgeons include short-acting anesthetics to facilitate early emergence, opioid-sparing analgesia, euvolemic fluid management, etc.[16] In achieving early emergence from general anesthesia and euvolemic status during surgery, we could add important evidence and provide useful clinical implication to ERAS protocols by elucidating the effectiveness of precision guidance of anesthesia depth and goal-directed

hemodynamic therapy using real-time spectral entropy and minimally invasive CO monitoring in thoracic anesthesia.

3. Criteria of Eligibility

We will enroll the patients undergoing video-assisted thoracotomy at Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan. Exclusion criteria will be age < 20 years, pregnancy, end-stage renal disease, emergency surgery, presence of circulatory shock needing vasoactive drugs before surgery, any diagnosis of aortic diseases, cerebral vascular diseases or trauma, and high-degree cardiac arrythmia (e.g. atrial fibrillation), uses of cardiac pacemaker or automated implantable cardioverter defibrillator, New York Heart Association functional classification 4, long-term use of psychiatric medications, intraoperative blood loss > 1 L, intraoperative blood transfusion, planned or unanticipated transferal to intensive care unit for postoperative mechanical ventilation, and patient refusal to participate.

4. Study Design

We will use the design of factorial parallel randomized controlled trial to conduct these two studies in the same patient group. A computer-generated list of randomizations (Research Randomizer, www.randomizer.org) will be used for these group allocations. We will use stratified randomization method to ensure random allocations of these two treatments (spectral entropy and ProAQT goal-directed therapy) in all patients.[17] Allocation will be concealed with sequentially numbered sealed opaque envelopes. The principal investigator will open the respective concealed envelope containing the patient allocation to the treatment arm on the day of surgery immediately before induction of anesthesia. In this trial, we will conform to the recommendations in the Consolidated Standards of Reporting Trials (CONSORT) statement.[18,19] In addition, we will follow the principle of intention-to-treat in our analyses of the trial results.

5. Study Methods

The effect of M-Entropy guidance of anesthesia depth on postoperative recovery: A single-blind randomized controlled trial

Standard monitoring will be applied, including five-lead electrocardiogram, pulse oximetry, capnography, radial artery catheterization for arterial blood pressure, and internal jugular vein cannulation for central venous pressure. Patients will be given balanced general anesthesia, including fentanyl 1–2 $\mu g \cdot kg^{-1}$ and propofol 1–2 $mg \cdot kg^{-1}$ for induction, and rocuronium 0.8 $mg \cdot kg^{-1}$ to facilitate tracheal intubation. Anesthesia will be maintained using sevoflurane 2–3 vol% in oxygen. An additional bolus of intravenous fentanyl 50 μg will be administered before surgical incision. Pressure-controlled ventilation with a positive end expiratory pressure of 5 cm H_2O and peak pressure < 30 cm H_2O will be applied for both double-lung ventilation and OLV. OLV will be initiated after patients are in the lateral decubitus position. During double-lung ventilation the inspiratory oxygen fraction will be set to 0.6, whereas 0.8–1.0 will be used for OLV to ensure oxygen saturation higher than 92%. For double-lung ventilation, tidal volumes up to 8 $ml \cdot kg^{-1}$ and a respiratory rate of 10–15 min^{-1} will be chosen, for OLV tidal volumes up to 6–7 $ml \cdot kg^{-1}$ with a respiratory frequency of 10–15 min^{-1} will be used. In both groups re-inflating of the previously non-ventilated lung will be restarted by a manual recruitment maneuver with peak pressure 30 cm H_2O for 10 s three times. Intravenous parecoxib 40 mg will be given promptly after induction of anesthesia, followed by parecoxib 20 to 40 mg every 12 hours for three days.

Intravenous as-needed analgesia with morphine and/or ketorolac will be used to relieve breakthrough pain, which will be switched to oral diclofenac on the postoperative 2nd or 3rd day.

In the M-Entropy group, dosage of volatile anesthetics will be adjusted to achieve the response and state entropy values between 40 and 60 from the start of anesthesia to the end of surgery. In the control group, dosage of volatile anesthetics will be titrated according to clinical judgment. This will be to maintain mean arterial pressure and heart rate within 20% range of the baseline. 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 control 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. After reversal of the neuromuscular blocking agent and response to verbal command, all subjects will be extubated at the operating room and then transferred to the postanesthetic care unit. In the postoperative period, surgeons, medical and nursing staff at the postanesthetic care unit will be blinded to group allocation.

Primary outcome is time to spontaneous eye opening. Secondary outcomes include time to tracheal extubation, time to orientation in time and place, time to leave operating room, and events of emergence agitation, postoperative delirium, and intraoperative recall or awareness. We will use the Richmond Agitation-Sedation Scale to evaluate the level of agitation and sedation promptly after extubation.[20] Events of delirium will be evaluated using the Confusion Assessment Method at the postanesthetic care unit 30 minutes after tracheal extubation.[21] An independent adjudicator blinded to the group allocation will measure all the outcomes.

The effect of application of ProAQT in guiding goal-directed hemodynamic therapy on postoperative recovery: A single-blind randomized controlled trial

In both groups, intraoperative maintenance rate of crystalloid fluids is 3 $ml \cdot kg^{-1} \cdot hr^{-1}$. ProAQT-derived hemodynamic data are acquired at three time periods: before surgical incision, during OLV and at the end of surgery. Subjects randomized to the GDT group will be managed according to the ERAS algorithm utilizing ProAQT variables (mean arterial pressure, stroke volume variation and cardiac index)[22,23] If stroke volume variation is ≥ 10%, a bolus of 150 ml of crystalloid fluid will be given until the stroke volume variation is < 10%. If mean arterial pressure is < 70 mmHg and/or cardiac index < 2.5 $l \cdot min^{-1} \cdot m^{-2}$ despite the stroke volume variation of < 10% following fluid challenge, single or consecutive boluses of ephedrine 4 mg and/or continuous intravenous infusion of norepinephrine 2–10 $\mu g \cdot min^{-1}$ will be administered. (Figure 1)

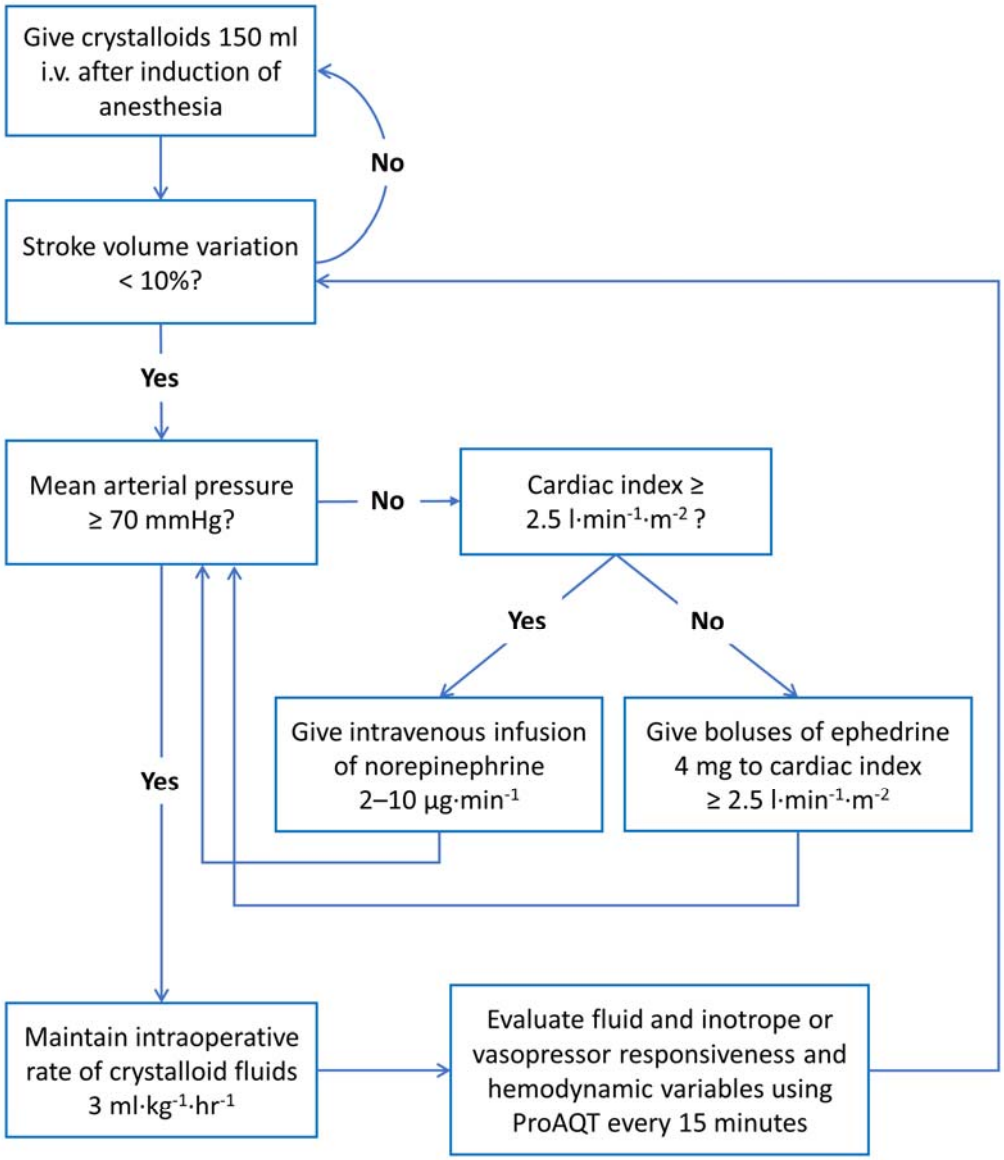

Figure 1: Goal-directed hemodynamic algorithm to guide intraoperative fluid therapy and the use of vasopressor and inotropic therapy in the goal-directed therapy group

Subjects allocated to the control group are hemodynamically managed as follows. Isolated hypotension (defined as 20% decrease in mean arterial pressure below baseline or < 60 mmHg) is treated by a continuous intravenous infusion of norepinephrine 2–10 µg·min^{-1}. If hypotension persists, repeat boluses of ephedrine 4 mg will be administered until mean arterial pressure is > 60 mmHg. If hypotension is accompanied by signs of hypovolemia (defined as urine output < 0.5 ml·kg^{-1}·hr^{-1} and/or an increase in heart rate > 20% above baseline), crystalloid fluid will be administered until urine output and/or heart rate are normalized. Colloids are administered only when hypotension develops during acute hemorrhage. If hypotension persists despite volume challenges, norepinephrine will be administered. In both groups, fluid and inotrope or

vasopressor responsiveness and hemodynamic variables will be evaluated each 15 min, and more frequently in case of hemodynamic instability. ProAQT variables will be recorded every 15 min.

The primary outcome is in-hospital postoperative pulmonary complication, including atelectasis, pleural effusion, pneumonia, empyema, pulmonary embolism, re-operation, and respiratory failure. The diagnosis of atelectasis and pleural effusion will be made based on routinely performed chest radiographs on postoperative days 1 and 3. Pneumonia will be diagnosed if a patient presents with fever, leukocytosis and new infiltrates on chest radiography. Pleural empyema and pulmonary embolism will be confirmed by spiral computed tomography scan. Respiratory failure is defined as described.[24] Secondary outcomes include relative change of PaO_2/FiO_2, PaO_2/FiO_2 values after induction of anesthesia and at the end of surgery, acute kidney injury (defined by Acute Kidney Injury Network Criteria),[25] cardiac complications (myocardial infarction diagnosed by electrocardiogram and troponin T serum concentration; newly developed atrial fibrillation), clinically relevant hypotensive episodes (decrease in mean arterial pressure > 20% for more than 15 min requiring vasopressors), newly developed stroke, and length of hospital stay. All outcomes will be determined again 30 days after surgery and documented by research staff blinded to group allocation.

Statistical Analysis

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 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).

References

1. Miller R: Miller's Anesthesia, 9th edition. Amsterdam, Elsevier Health Sciences, 2019, pp.1648.
2. Mashour GA, Avidan MS. Intraoperative awareness: controversies and non-controversies. *Br J Anaesth*. 2015;115:i20-6.
3. Miller R: Miller's Anesthesia, 8th revised edition. Amsterdam, Elsevier Health Sciences, 2014, pp.1056.
4. Short TG, Campbell D, Frampton C, Chan MTV, Myles PS, Corcoran TB, et al. Anaesthetic depth and complications after major surgery: an international, randomised controlled trial. *Lancet*. 2019;394:1907-1914.
5. Drummond KE, Murphy E. Minimally invasive cardiac output monitors. *Continuing Education in Anaesthesia Critical Care & Pain*. 2012;12:5-10.
6. Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. *Cochrane Database Syst Rev*. 2019;9:CD003843.
7. Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. *Br J Anaesth*. 2019;123:e312-21.
8. Chhabra A, Subramaniam R, Srivastava A, Prabhakar H, Kalaivani M, Paranjape S. Spectral entropy monitoring for adults and children undergoing general anaesthesia. *Cochrane Database Syst Rev*. 2016;3:CD010135.
9. Kobe J, Mishra N, Arya VK, Al-Moustadi W, Nates W, Kumar B. Cardiac output monitoring: Technology and choice. *Ann Card Anaesth*. 2019;22:6-17.
10. Gómez-Izquierdo JC, Trainito A, Mirzakandov D, Stein BL, Liberman S, Charlebois P, et al. Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery: A Randomized Controlled Trial. *Anesthesiology*. 2017;127:36-49.
11. Raphael J, Regali LA, Thiele RH. Hemodynamic monitoring in thoracic surgical patients. *Curr Opin Anaesthesiol*. 2017;30:7-16.
12. Hung MH, Chen JS, Cheng YJ. Precise anesthesia in thoracoscopic operations. *Curr Opin Anaesthesiol*. 2019;32:39-43.
13. Kaufmann KB, Stein L, Bogatyreva L, Ulbrich F, Kaifi JT, Hauschke D, et al. Oesophageal Doppler guided goal-directed haemodynamic therapy in thoracic surgery - a single centre randomized parallel-arm trial. *Br J Anaesth*. 2017;118:852-61.
14. Pedoto A, Perrino AC Jr. Delayed recovery following thoracic surgery: persistent issues and potential interventions. *Curr Opin Anaesthesiol.* 2019;32:3-9.
15. A Mesbah, J Yeung, F Gao. Pain after thoracotomy. *BJA Education.* 2016;16:1-7.
16. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg.* 2019;55:91-115.
17. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. *J Clin Epidemiol*. 1999;52:19-26.
18. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152:726-32.

19. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P; CONSORT NPT Group. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167:40-47.
20. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289:2983-91.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113:941-8.
22. Feldheiser A, Conroy P, Bonomo T, Cox B, Garces TR, Spies C. Development and feasibility study of an algorithm for intraoperative goal-directed haemodynamic management in noncardiac surgery. *J Int Med Res*. 2012;40:1227-41.
23. Suehiro K, Okutani R. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing one-lung ventilation. *J Cardiothorac Vasc Anesth*. 2010;24:772-5.
24. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol*. 2015;32:88-105.
25. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11:R31.
26. Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks/Cole; 2011.