A study of lung ultrasound combined with oxygenation index for precise extubation after general anaesthesia in the elderly - a multicentre, randomised, double-blind clinical trial

Programme number: V4.0

Team leader: Tianjin First Central Hospital

Principal Investigator: Lili Jia

Version date: 2022.11.4

Principal Investigator Programme Signature (Team Leader Unit)

Protocol name: Study of pulmonary ultrasound combined with oxygenation index for precise extubation after general anaesthesia in the elderly - a multicentre, randomised, double-blind parallel controlled clinical trial

Programme code: 20221104

Version number and date: 4.0, 4 November 2022

By signing this programme signature page, the investigator acknowledges and agrees that.

I have read the above research proposal and its annexes.

I agree to carry out the study in accordance with this study protocol and the ICH-GCP, local regulations and other applicable regulations to perform the relevant duties.

This document contains confidential information and will not be disclosed without written authorisation from the reporting party, except to those directly involved in the execution of the study or ethical/regulatory review.

I agree that I will ensure that all staff involved in this study are aware of their obligations in relation to the above commitments.

Research Unit: Tianjin First Central Hospital

Lily Jia

---------- ---------- ----------

Principal Investigator (in print) Principal Investigator (signature) Date of signature (year/month/day)

Programme Summary

Study Title	A study of lung ultrasound combined with oxygenation index for precise extubation after general anesthesia in the elderly - a multicenter, randomized, double-blind clinical trial.
Programme number	20221104
Version number and date	V4.0, 2022.11.04
Principal Investigator	Tianjin First Central Hospital, Jia Lili
Senate Research Centre	5 tertiary hospitals
Purpose of the study	**Main research objectives** 1. to evaluate the predictive value of LUS, MAPSE, TAPSE, DD and OI indicators for accurate postoperative extubation in elderly people undergoing general anaesthesia. 2. Explicit cardiac and pulmonary ultrasound combined with diaphragmatic mobility and oxygenation index is a good guide to cardiac and pulmonary complications after surgery in the elderly.
Study endpoints	The incidence of pulmonary complications at 7d postoperatively and mortality in patients at 30d postoperatively.
Study population	Elderly patients admitted to the PACU with a tube after major surgery under general anaesthesia, aged ≥65 years, expected to be mechanically ventilated for ≥3h and who have passed the clinician's withdrawal screening test.
Study design	We joined hands with the Fourth Central Hospital of Tianjin, the Fifth Central Hospital of Tianjin, the TEDA Hospital of Tianjin, the First Hospital of Shanxi Medical University and the Cancer Hospital of Shanxi Province to conduct a multicentre prospective clinical trial of 200 elderly patients, aged ⩾65 years, after general anaesthetic surgery. Ultrasound examinations of the heart and lungs were performed on elderly post-operative patients who had passed the SBT trial and needed to be extubated. LUS, MAPSE, TAPSE and DD were calculated, and arterial blood was drawn to determine OI using a blood gas analyser. The ROC curves of the combined predictors of LUS, MAPSE, TAPSE, DD and OI were plotted, the area under the curve (AUC) was calculated, the optimal threshold value was selected, the sensitivity and specificity were calculated, and the predictive value of the above indicators was evaluated.

General information and clinical indicators: for elderly patients admitted to the resuscitation room after general anaesthesia, record the patient's name, gender, age, pH at the end of the SBT test, PaO_2 /FiO_2 , PaO_2 , $PaCO_2$, tidal volume.

222 The patient's heart rate, respiration, blood pressure, tidal volume and other parameters are recorded, as well as the patient's subjective response (presence or absence of dyspnoea). After extraction, another arterial blood gas is drawn and the arterial partial pressure of oxygen is analysed, as well as the inhalation oxygen concentration, respiratory rate and exhalation tidal volume. Calculate the oxygenation index (P/F value) = arterial partial pressure of oxygen (PaO_2)/inhaled oxygen concentration (FiO_2).

Withdrawal Screening Test (SBT).

(1) The cause of the mechanical ventilation has improved or been removed.

(2) Oxygenation indicators: oxygenation index ≥150~ 300; PEEP ≤5~ 8cmH_2 O; FiO_2 ≤0.4; pH ≥7.25; for patients with COPD: pH >7.30, FiO_2 <0.35, PaO_2 >50mmHg.

(3) Haemodynamic stability, absence of dynamic changes in myocardial ischaemia and absence of significant hypotension.

(4) The patient has the ability to breathe spontaneously and the respiratory centre is able to maintain a spontaneous respiratory rhythm.

Lung ultrasound tests.

At the end of the SBT, the same group of attending physicians with extensive ultrasound experience performed bedside ultrasound using a body-surface zone-based lung ultrasound scoring method according to the guidelines for the clinical application of critical care ultrasound published by the China Critical Care Ultrasound Research Group. A wide-frequency convex array probe was selected and the patient was placed in the supine position, and the anterior, lateral and posterior chest walls of both sides of the patient were examined using the 12-lung differentiation method.

LUS Rating:

(1) Normal ventilation zone: 0 points for lung sliding sign with A-line or <3 separate B-lines; (2) Moderately reduced lung ventilation zone (B1): 1 point for multiple, typical B-lines; (3) Severely reduced lung ventilation zone (B2): 2 points for multiple fused B-lines.

(4) Pulmonary solid zone (C): tissue image with typical bronchial congestion, 3 marks.

The LUS score is the sum of the 12 regional lung scores, with each regional score being the most severe performance score for that region, measured over 5 min.

Transthoracic cardiac ultrasonography.

The patient's apical four-chamber view was obtained using M-mode ultrasound, with the M-mode ultrasound sampling line parallel to the septum as far as possible, and the sampling point located at the junctional tangent between the posterior mitral annulus and the left

	ventricular free wall to obtain a clear image of the mitral annular motion displacement, freeze and magnify this image, and measure the maximum mitral annular displacement (MAPSE) from end-diastole to end-systole. In the same way, the M-mode ultrasound sampling line was placed parallel to the ventricular septum as far as possible, at which point the sampling point was located at the tangent of the junction between the anterior tricuspid annulus and the free wall of the right ventricle, and the maximum end-diastolic to end-systolic displacement (TAPSE) of the tricuspid annulus was measured. After three consecutive measurements, the mean of these two parameters is calculated and the difference between them is then calculated to give the difference in annular plane systolic excursion difference (APSED) between the mitral and tricuspid annuli. (The normal value for TAPSE is 22-24 mm; for MAPSE the normal value is ⩾13 mm in men and ⩾11 mm in women.) **Diaphragm mobility check:** The patient was placed in a supine position, with the chest and upper abdomen exposed. After stable breathing, an ultrasound convex array probe was used to detect under the rib arch in the right midclavicular line, and the distance between the diaphragm and the body probe was recorded in M ultrasound mode, and the difference between the diaphragm movement in the inspiratory and expiratory phases was measured at the end of the SBT test and recorded as DD. The group was divided into a successful extraction group and a failed extraction group according to the outcome of the withdrawal. The criteria for successful extubation are as follows: observe the withdrawal of extubation for 48 h. Signs of respiratory distress, i.e. increased respiratory rate (RR), increased heart rate (HR) and decreased oxygen saturation (SpO_2) within 48 h. The need for non-invasive mechanical ventilation or high-flow nasal cannula oxygen therapy or even reintubation is considered a failure of extubation, otherwise the extubation is considered successful. The incidence of cardiac and pulmonary complications at 7d postoperatively and the mortality rate of patients at 30d postoperatively were recorded.
Entry criteria	(1) Age ⩾ 65 years, regardless of gender. (2) Post-tracheal intubation, ventilator-assisted ventilation. (3) Performing general anaesthetic surgery. (4) Duration of mechanical ventilation ⩾ 3h. (5) Successfully passed the Spontaneous Breathing Test (SBT).
Exclusion criteria	(1) Narrowing of the airway and compression of the airway. (2) Large breaks and burns to the skin of the chest. (3) Central respiratory failure. (4) Severe muscle weakness and absence of voluntary diaphragmatic activity. (5) Patients with unscheduled extubation. (6) Patients with combined end-stage cardiopulmonary disease.

Exit criteria	Termination of the trial is required if the subject meets one or more of the following criteria. (1) Complications that endanger the life of the patient and require urgent resuscitation. (2) The subject or guardian requests to withdraw from the trial. (3) Other circumstances that, in the judgment of the investigator, warrant withdrawal from the trial.
Determination of sample size	Two hundred subjects were to be enrolled in this study and divided into a successful extubation group and a failed extubation group according to the final extubation outcome. As there is no previous literature assessing the value of combined cardiopulmonary and diaphragmatic indicators to predict extubation, it was not possible to calculate a formal sample size, referring to previous literature examining the effect of single factors and the pre-trial main efficacy indicator of successful extubation, which was 70% for the conventional group and 100% for the pulmonary ultrasound group. The software PASS (version 21.0.3) was used to calculate that 166 patients were required for this trial at the 0.05 (one-sided) significance level. (taking into account a 10% shedding rate), which provides a 90% certainty test to obtain validity results for the test group compared to the conventional group.
Statistical analysis	The general principles of descriptive statistical analysis in this study were as follows. SPSS 22.0 was used for statistical analysis. Continuous measures were expressed as ($\bar{x} \pm s$) and tested for normality, and independent samples t-test was used for comparison of normally distributed data between the two groups. The χ^2 test was performed for statistical data to verify whether there was a statistical difference between the groups. $p<0.05$ was statistically different. Logistic regression model analysis was applied to derive prediction models for lung ultrasound score, diaphragm mobility and oxygenation index. ROC curves were plotted for lung ultrasound score, transthoracic cardiac ultrasound, diaphragm mobility, oxygenation index and the combined predictors, the area under the curve (AUC) was calculated for the subjects, the best cut-off value was selected, sensitivity and specificity were calculated and the predictive value of the above indicators was evaluated.

Informed Consent Form

(for non-interventional clinical studies, e.g. interviews, surveys, observational studies)

Dear Madam/Mr.

We invite you to participate in the research project "Application of pulmonary ultrasound combined with oxygenation index in precise extubation after general anaesthesia in the elderly" approved by the Tianjin Anesthesia Research Development Programme (based on the Bai Qiu'en Public Welfare Foundation). The study will be conducted in five hospitals, namely Tianjin First Central Hospital, Tianjin Fourth Central Hospital, Tianjin Fifth Central Hospital, Tianjin TEDA Hospital, First Hospital of Shanxi Medical University and Shanxi Cancer Hospital, and an estimated 200 subjects will volunteer to participate. The study has been reviewed and approved by the Ethics Committee of Tianjin No. 1 Central Hospital. The Ethics Committee is an independent committee consisting of a group of independent experts and lay people whose purpose is to help the subjects protect their rights. This does not mean, however, that this study is free from any risk.

1. Introduction: Why did we invite you to participate in the study?
   You are invited to participate in this study because you are ≥65 years of age, are having a major general anaesthetic procedure and are on mechanical ventilation for more than 3 hours and meet the inclusion criteria for this trial.
2. Do you have to participate in this study?
   It is up to you to decide whether or not to participate in the study. You may refuse to participate at any time and we will not change your usual treatment as a result. If you participate in this study, you can also withdraw at any time.
3. Why was this study conducted?
   The aim of the study is that the incidence of failed extubation accounts for 10-15% of mechanical ventilation, and this incidence is further increased in the elderly. To explore the value of applying cardiopulmonary ultrasound combined with oxygenation index to guide the timing of extubation after general anaesthesia and to help anaesthetists to extubate efficiently and successfully; to clarify the value of cardiac and pulmonary ultrasound combined with diaphragmatic mobility and oxygenation index as a better guide to cardiopulmonary complications after surgery in the elderly.
4. How will the research be conducted?
   Before you are extubated, MAPSE, TAPSE, lung ultrasound score and diaphragm mobility are measured using ultrasound and arterial oxygenation index is measured using a blood gas analyser before you are extubated. We will record the occurrence of your cardiac and pulmonary complications 7 days after surgery and for 30 days afterwards by means of an electronic case system and telephone follow-up visits, each of which will take 5 minutes.
   How long will you be involved in the study?
   You will participate in the study from the start of your anaesthetic to the end of your surgery when you are admitted to the recovery room for observation and for 30 days after your surgery.
5. Can you withdraw from the study?
   You can withdraw from the study at any time, and please inform the researcher.
   The researcher may terminate the study on you at any time for any reason and will inform you of this.
6. What risks do you encounter in your research?
   This is an observational clinical study and all ultrasound examinations are non-invasive and post-operative blood gas analysis is a normal routine medical test. Therefore, there is no risk to you during the study, but there is still a risk that you may have to undergo mechanical ventilation again.
   Another risk is the disclosure of confidentiality. We will meet our due diligence obligations with regard to your research records.
7. What are your possible benefits?
   You may benefit from the information obtained in this study by.
   (1) Patients can receive better care and attention in terms of hospitalisation, investigations, treatment and follow-up, and any situation that requires urgent attention can be dealt with quickly. (2) Although there is no prospect of direct benefit to subjects from such studies, they can help guide precise extubation and reduce postoperative cardiopulmonary complications in elderly patients.
8. Do you need to pay to participate in this study?
   There is no cost to you in this study.
9. Will you be compensated for your participation in this study?

We will not compensate you for participating in this study.

10. Can you receive compensation for injuries suffered as a result of participating in this study?
    The study is an observational clinical study and the operation is non-invasive and does not cause any additional harm to the patient, therefore no compensation has been made to the patient.
11. Who should you contact if you have a query?
    If you have any questions related to this study, please contact the Department of Anaesthesia (Jia Lili) of the First Central Hospital of Tianjin directly at 13102058301. If you have any questions about the rights of the subjects, or if you have any complaints or suggestions, please contact the office of the Ethics Committee at 022-23626468.
    What medical information will we be collecting?
    We need your permission to collect some medical information about you. If you refuse to provide medical information, you will not be able to participate in the study. This information will come from our questions, forms you fill in or your medical records as described below. We will only collect information that is necessary for the study.
    For example, the questionnaire used for the study.
    Laboratory tests and relevant imaging data from the date of your entry into the study until your discharge from hospital.
    Who will have access to your medical information?
    Only our staff involved in clinical research, members of the ethics committee and those involved in overseeing research activities in accordance with our rules and regulations are allowed access to your medical information.
    The research team will share your medical information with the following organisations who are collaborating with us or funding the study.
    Tianjin Anesthesia Research Development Program - Baiqiuen Public Welfare Foundation
    Tianjin First Central Hospital
    Tianjin Fourth Central Hospital, Tianjin Fifth Central Hospital, Tianjin TEDA Hospital, First Hospital of Shanxi Medical University, Shanxi Cancer Hospital
    We will record medical information about your stay at our hospital, including the results of tests, examinations and research questionnaires. This information may be read by the relevant authorised person for the purpose of treating you. It may also be read by someone who has your/guardian's written consent, or who is permitted by law to read your information.
    We will not use this information for different studies without your permission, or the permission of the ethics committee.
    Once this information has been de-identified in the future, it can be used for other purposes without asking for your opinion. The results of the research will be published publicly (in a public presentation or in writing), but any information that identifies you will not appear.
12. What are the risks of sharing medical information?
    One of the risks of taking part in the study is that more people will have access to your medical information. The research team will make every effort to protect information about you, but it is possible that some unauthorised people may also be able to see your information. This may embarrass you or affect your access to medical insurance. You can discuss with the principal investigator whether you are at risk of this.
13. How long will we keep your medical information?
    We will keep this information indefinitely so that it can be accessed again in the future.
14. Can you cancel your previous commitment to agree to share medical information?
    If you change your mind and do not want us to collect and share your information Please write to the principal investigator, Tianjin First Central Hospital, 24 Fukang Road, Nankai District, Tianjin, China. This letter should state that you have changed your mind and do not want us to collect and share your information. At that time we may decide to terminate your participation in the study, but we may continue to use the information we have collected about you.

Consent to participate in the study

Before signing, I confirm the following facts.

- I have read (or have had read aloud to me) the entire consent document. All my questions have been answered to my satisfaction.
- The purpose of the study, the procedures, and the possible benefits and risks have been explained to me by the researcher.
- I agree to allow the research team to use and share my medical information and other information gathered from the study.
- I volunteer to participate in this study. I agree to follow the study procedures as required. I have been informed that I can withdraw from the study at any time.

Please note: You will be provided with a signed and dated copy of this consent form. Please keep this consent form in a safe place where you can easily find it. It will help you to remember what we have discussed today.

Subject's signature: Date: _____ Month of _____ Year
Subject's contact number: Mobile no.

Signature of legal representative: Date: _____ Month of _____ Year
Contact number of the legal representative: Mobile no.

Signature of researcher: Date: _____ Month of _____ Year
Researcher's working telephone number: Mobile number

Tianjin First Central Hospital Science and Technology Ethics Committee Office Contact: 022-23626468