Ultrasound assessment of aeration changes after lung resection via VATS: a pilot study

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Brief summary

The purpose of the study is to assess whether lung ultrasound is able to detect lung injury after lung resection surgery.

Detailed description

Postoperative pulmonary complications (PPC) are common after lung resection surgery, with an incidence that ranges between 11-32%. As PPC are associated with worse outcomes, many studies aim to find predictors that identify high risk patients and prompt specific interventions and/or monitoring and hence, improve outcomes. PPC result from lung injury inherent to lung resection surgery. Lung aeration changes seen with lung ultrasound (LUS) could detect lung injury and thus, identify patients at high risk of PPC. The underlying mechanisms of lung injury are different in the dependent and non-dependent lung; oxidative stress in both lungs, lung injury associated with one-lung ventilation in the dependent lung and ischemia/reperfusion or surgical manipulation in the non-dependent lung. LUS evaluates the dependent and non-dependent lung separately and so it can be valuable in understanding the characteristics and intensity of lung injury in each lung specifically.

This is a prospective, single-centre, observational study in which 30 consecutive participants with non-small cell lung cancer scheduled for lung resection via VATS will be recruited. Participants will be divided in two groups depending on the size of the resection. First group will be resection less than lobectomy. Second group will be resection equal to or greater than lobectomy. Participants will be recruited consecutively until there are 15 patients in each group. LUS will be performed in each participant's operated and non-operated lung at three predefined time points: before surgery, after extubation and 24 h after surgery. Each hemithorax will be divided into 6 areas: anterior, lateral and posterior, separated by the anterior and posterior axillary lines, each divided into upper and lower zones. For each echographic examination, cineloops of the most pathological findings in each area will be stored and analysed offline by two independent and blinded anaesthesiologists. From these, a semiquantitative score, the modified lung ultrasound score (mLUSS), will be calculated for each hemithorax to assess lung aeration at each time point. The level of agreement for mLUSS will be tested. At the same predefined time points blood plasma samples will be collected, flash-frozen and stored in order to measure levels of the inflammatory mediators IL-6, IL-10 and TNFα.

The investigators hypothesise that LUS can detect lung injury after lung resection surgery. The primary objective of the study is to assess changes in lung aeration after lung resection with mLUSS. Secondary objectives are, first, to describe LUS findings after lung resection surgery, second, to assess the ability of mLUSS to detect oxygenation changes after lung resection and third, to compare the behaviour of inflammatory mediators in plasma with mLUSS changes.

Outcome measures

1. Primary outcome measure

Title: change in mLUSS after lung resection. Description: the modified lung ultrasound score (mLUSS) ranges 0-36; the higher the score, the less aeration (worse). Timeframe: preoperative vs immediate postoperative period vs 24 hours after surgery.

2. Secondary outcome measures

- Title: LUS findings in the dependent and non-dependent lung. Description: description of LUS findings after lung resection surgery in each lung. Timeframe: preoperative vs immediate postoperative period vs 24 hours after surgery.

- Title: changes in oxygenation (PAFI) after lung resection. Description: PAFI is the ratio between paO2 and fraction of inspired oxygen; the lower, the worse. Timeframe: preoperative vs immediate postoperative period vs 24 hours after surgery.

- Title: changes in plasma cytokine IL-6 after lung resection. Timeframe: preoperative vs immediate postoperative vs 24 hours after surgery.

- Title: changes in plasma cytokine IL-10 after lung resection. Timeframe: preoperative vs immediate postoperative vs 24 hours after surgery.

- Title: changes in plasma TNFα after lung resection. Timeframe: preoperative vs immediate postoperative vs 24 hours after surgery.

- Title: changes in blood bone natriuretic peptide (BNP) after lung resection. Timeframe: preoperative vs immediate postoperative vs 24 hours after surgery.

Methods

This study was first approved by the Clinical Investigation Ethics Committee of the General University Hospital of Valencia on 25th October 2018, with a later amendment approved on 6th November 2020, before the beginning of recruitment.

1. Study groups

This is a prospective, single-centre, observational study in which 30 consecutive participants with non-small cell lung cancer scheduled for lung resection via VATS will be recruited. Participants will be divided in two groups depending on the size of the resection. First group will be resection less than lobectomy. Second group will be resection equal to or greater than lobectomy. Participants will be recruited consecutively until there are 15 patients in each group. Sample size has not been calculated, as there is no previous information on changes in lung aeration after lung resection. Sample size will be set in 28 participants, adding 5% (30 participants in total) to compensate for possible losses.

2. Elegibility

- Inclusion Criteria:

Age > 18
ASA I-III
Non-small cell lung neoplasm
Elective lung resection
Via VATS
Under one-lung ventilation

- Exclusion Criteria:

Pregnancy
Respiratory tract infection the previous month
Diagnosed pulmonary fibrosis
Predicted FEV < 40%
Surgery limited to biopsy
Surgery that includes resection of the thoracic wall or the diaphragm
Neoplasm metastasis
Obesity class II or more (BMI ≥ 35 kg/m^2)
Risk of malnutrition CONUT > 1
Hemoglobin < 10 g/dl
Chronic kidney failure: glomerular filtration < 60 ml/min/m^2, nephrectomy, kidney transplantation
Treatment with corticosteroids or immunosuppressive agents 3 months before surgery
Transfusion of blood products during the previous 10 days
Heart failure (New York Heart Association Functional Class 3 or 4) during the week before surgery.
Heart valve diseases over stage B of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2014
Diastolic dysfunction

Recruited participants will be excluded in the following cases:

Intraoperative or postoperative blood product transfusion (first 24 h)
Pleurodesis
Need to convert to thoracotomy

3. Study protocol

Baseline characteristics

The following demographic data will be collected: age, sex, height, weight, BMI, malnutrition universal screening tool (MUST) score and CONUT nutrition score, American society of anaesthesiologists (ASA) status, and ARISCAT score.

Information regarding comorbidities will include the following: hypertension, diabetes, myocardial ischemia, NYHA, EPOC GOLD score, asthma, obstructive sleep apnoea (OSA), smoking state and alcohol intake.

The following data regarding pulmonary function testing will be included: forced expiratory velocity (FEV1), forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO) and peripheral oxygen saturation (SpO2) breathing room air.

In addition to this, heart rate and median arterial pressure will be recorded.

Preoperative evaluation

This will include the following examinations (explained at the end of the protocol):

- ultrasound including lung, diaphragm and echocardiography.
- blood analysis for measurement of inflammatory mediators, as well as blood count and chemistry.
- chest X-ray

Anaesthesia protocol

Analgesia will be administered via a paravertebral catheter in the non-dependent hemithorax of participants undergoing a resection equal to or greater than lobectomy, with an initial dose of 0’25% levobupivacaine (0’3 ml/kg) followed by subsequent boluses of 0’25% levobupivacaine 6-10 ml every hour. Analgesia will be administered via an erector spinae single shot block in the non-dependent hemithorax of participants undergoing rection less than lobectomy, with 0’25% levobupivacaine (0’3 ml/kg) plus infiltration of the ports at the end of the procedure with levobupivacaine 0’25%. Anaesthesia will be induced with propofol (2 to 3 mg/kg) and fentanyl (2-3 mcg/kg). Neuromuscular blockade will be achieved with rocuronium (0.6 to 1 mg/kg). Orotracheal intubation will be performed with a left double-lumen tube (35 to 37 Fr in women and 39 to 41 Fr in men). Correct placement will be verified by direct visualisation with a fibreoptic bronchoscope. All patients will be managed using a Perseus ventilator (Drägerwerk). Volume-controlled ventilation will be used during two-lung ventilation (TLV) with the following parameters: tidal volume 7 ml/kg (predicted body weight); inspiratory pause 25%, positive end-expiratory pressure (PEEP) 5cmH2O; fraction of inspired oxygen (FiO2) 0.4 to 0.5; and respiratory

rate to maintain end-tidal carbon dioxide pressure (ETCO2) at 35 to 45 mmHg. Hypnosis will be maintained with sevoflurane at the necessary concentrations to maintain a bispectral index of between 40 and 60. A continuous infusion of rocuronium will be used to achieve profound neuromuscular blockade with train of four (TOF) of 0. A continuous infusion of remifentanil 0.1-0.3 mcg/kg/min will be used to achieve hemodynamic stability after having administered levobupivacaine through the paravertebral catheter, in the cases where there is a catheter. Intermittent pneumatic compression stocks and convective warming blanket will be systematically used.

OLV will be undertaken using volume-controlled ventilation and the following parameters: tidal volume 5 ml/kg (predicted body weight); inspiratory pause 25%, PEEP 5cmH2O; permissive hypercapnia; and FiO2 0.6 to 1 in order to maintain oxygen saturation (SaO2) more than 90%. A recruitment manoeuvre (RM) will be systematically performed after the initiation of OLV and the ensuing optimal PEEP will be set. Another RM will be systematically performed after reinitiating TLV at the end of the surgery. The application of further recruitment manoeuvres or continuous positive airway pressure (CPAP) to the non-dependent lung will be instituted in the event of hypoxemia. Restrictive intravenous fluid therapy will be used, with fluids given at 2 ml/kg/ h in order to maintain urine output 0.5 ml/kg/h. Fluid administration will be recorded; crystalloids and colloids. Urine output, the use of diuretics (drug and dose), the estimated blood loss and overall fluid balance will also be recorded.

At baseline during TLV, at 10 min after RM in OLV and at 10 min after RM in TLV data regarding haemodynamic monitoring, ventilation and blood gas exchange will be recorded, as explained below.

The radial artery will be catheterised in all cases (FloTrac Sensor; Edwards Lifesciences Corp., Irvine, California, USA) for intraoperative monitoring of continuous cardiac index, stroke volume variation, stroke volume index and invasive arterial pressure.

Registered data regarding ventilation will be recorded as follows; FiO2; peripheral oxygen saturation (SpO2); ETCO2; tidal volume (TV); respiratory rate; peak, plateau, mean, driving and end-expiratory airway pressures; and lung compliance.

Arterial blood will be drawn for measurement of respiratory gases (pH, paO2, paCO2) and lactate.

Attending surgeon, duration of anaesthesia, total dose of opioids given, duration of surgery, extent of lymphatic resection and weight of the resected piece will also be recorded.

The intraoperative complications considered relevant for the study will be registered and include: desaturation (SpO2 < 90% more than 2 minutes), hypotension (PAS < 90 mmHg or PAM < 65 mmHg more than 3 minutes) and new onset arrhythmia (atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation). If there is need of infusion of vasoactive drugs, the drug and cumulative dose will also be registered.

At the end of the surgery, neuromuscular blockade will be reversed with sugammadex for a TOFr> 0’9 before extubation. Participants will then be transferred to the ICU or PACU with supplemental oxygen FiO2 0.4 through a venturi mask.

Postoperative course: Immediate postoperative period

Depending on factors related to surgery and to participants, postoperative care will take place in the ICU or PACU.

At their arrival at ICU or PACU, chest drains will be connected to aspiration -20 cmH2O, and for those participants in whom there is an indwelling paravertebral catheter, continuous infusion of levobupivacaine 0'125% at 10-12 ml/h will be used until 72 h after surgery.

Examinations will include the following (explained at the end of the protocol):

- ultrasound including lung, diaphragm and echocardiography.
- blood analysis for measurement of inflammatory mediators, as well as blood count and chemistry.
- chest X-ray

The following data will be registered: SpO2, FiO2, heart rate, median arterial pressure, analgesia using visual analogue scale (VAS) at rest and presence of air leak through chest drains.

All participants will receive supplemental oxygen FiO2 0.4 through a venturi mask at least during the first postoperative hour. 15-30 minutes after arrival at ICU, if the participant is fully awake with Glasgow comma scale (GCS) > 13, is not agitated with Richmond Agitation-Sedation Scale (RASS) -1 to +1, has adequate analgesia level VAS < 4 and SpO2 ≥97% with venturi mask FiO2 0.4, an Air-Test will be performed. Oxygen mask will be removed and participants will be left breathing room air for at least 5 min while continuously monitoring SpO2. The Air-Test will be considered positive when the recorded SpO2 is ≤96% and negative when SpO2 is ≥97%. The oxygen mask will be placed back whenever SpO2 falls to 92% for more than 1 min during the Air-Test. Once the Air-Test is completed an arterial blood gas analysis will be done while breathing room air. Incentive spirometry will then be started.

Postoperative course: 24 hours after surgery

Participants who were admitted to the ICU will be transferred to the ward as per standard practice if the postoperative course is uneventful. Before being transferred data will be recorded. For participants who were not admitted to the ICU and were transferred to the ward after PACU vigilance, the same data will be recorded.

Examinations will include the following (explained at the end of the protocol):

- ultrasound including lung and diaphragm.
- blood analysis for measurement of inflammatory mediators, as well as blood count and chemistry.
- chest X-ray

The following data will be recorded: SpO2, FiO2, heart rate, mean arterial pressure, SAPS II, presence of air leak through the chest drains, administered fluids (crystalloids, colloids and blood products), urine output, use of diuretics (drug and dose), estimated blood loss and overall fluid balance. If there has been need of infusion of vasoactive drugs, the drug and cumulative dose.

Regarding analgesia, the following data will be collected: VAS at rest and during coughing, total dose of given opioids, infusion on levobupivacaine 0'125% through paravertebral catheter.

Regarding pulmonary function, the best result of incentive spirometry (0, 1, 2 or 3 balls lifted) will be recorded and participants will be inquired about dyspnoea (none, mild, moderate or severe).

Postoperative pulmonary complications may be correlated with the initial lung inflammatory response and will be recorded during the first postoperative week: [atelectasis, pneumonia, respiratory failure, reintubation, acute respiratory distress syndrome (ARDS), pleural effusion, pneumothorax, bronchospasm], as well as cardiological complications, surgical haemorrhage, acute kidney injury, length of stay in the ICU, length of hospital stay, reoperation during the first 14 days, readmission in the ICU during the first 14 days, readmission in the hospital during the first 30 days and mortality at 30 and 90 days.

Detailed examinations

-Ultrasound

Lung ultrasound (LUS) will be performed in each participant's dependent and non-dependent lung. Participants will be placed in a semi-recumbent position. Each hemithorax will be divided into 6 areas: anterior, lateral and posterior, separated by the anterior and posterior axillary lines, each divided into upper and lower zones. First, for each zone, subcutaneous emphysema (no emphysema, mild or moderate) and the feasibility of ultrasound evaluation (feasible, non-feasible) will be deemed. The focus will be set just below the pleural line. For each echographic examination, the most pathological area will be evaluated. The pleural line will be assessed for mobility (no mobility, lung pulse or lung sliding) and shape (regular or irregular). Specifically, the pleural line will be checked on the 2^{nd} and 3^{rd} intercostal space to assess the presence and extent of pneumothorax. B-lines will be counted (0-10) and lung consolidations (none, subpleural, translobar) will be looked for. A semiquantitative score, the modified lung ultrasound score (mLUSS), will be calculated for each hemithorax to assess lung aeration at each time point. The presence and size of pleural effusion will also be assessed in the most dependent region for each hemithorax. Cineloops will be stored and analysed offline by another independent and blinded anaesthesiologist. The level of agreement for mLUSS will be tested.

Diaphragm thickening fraction will be assessed at the zone of apposition located in the mid-axillary line between the eight and tenth ribs in a semi-recumbent position. Thickness will be measured from the inside edge of the diaphragmatic pleura to the inside edge of the peritoneal membrane at the end-expiration (EE) and end-inspiration (EI). The percent change in diaphragmatic thickness will be calculated by ([thickness at EI - Thickness at EE]/Thickness at EE).

Hand-held echocardiography will be performed. Feasibility will be deemed (feasible, non-feasible). Ejection fraction of the left ventricle will be visually assessed (normal function, mild or moderate dysfunction). Left heart preload and diastolic function will be evaluated with the following parameters: E wave, A wave, E/A, e' wave, E/e' and lateral S' wave. Right heart systolic function will be evaluated with lateral S' wave.

-Blood analysis

Inflammatory mediators interleukin (IL)-6, IL-10 and TNFα will be measured. Plasma samples will be collected, centrifuged and the supernatant flash-frozen and stored until assayed. Concentrations of the inflammatory markers will then be analysed using multiplex.

Blood count and chemistry will assess the following parameters: haemoglobin, leucocytes, lymphocytes, proteins, albumin, creatinine and glomerular filtration, bone natriuretic peptide (BNP), high sensitivity cardiac troponin T, c-reactive protein and procalcitonin. In addition to this, at baseline also lymphocytes, albumin and total cholesterol will be registered, in order to assess initial nutritional status (CONUT score).

Arterial blood will be drawn to analyse respiratory gases (pH, paO2, paCO2) and lactate.

-Chest X-ray

Chest x rays will be evaluated by a radiologist blinded to the clinical course to determine whether there is interstitial oedema, consolidation, pleural effusion or pneumothorax.