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Impact of continuous oxygen flow application with or without airway pressure in the non-dependent lung during one-lung ventilation on postoperative complications in lung resection surgery: a randomized controlled clinical trial

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Study protocol

Keywords: One-Lung Ventilation, Apneic Oxygenation, Continuous Positive Airway Pressure, Pulmonary Resection Surgery, Inflammation, Postoperative Complications

Posted Date: November 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8870781/v1

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Additional Declarations: No competing interests reported.

Title: I*mpact of continuous oxygen flow application with or without airway pressure in the non-dependent lung during one-lung ventilation on postoperative complications in lung resection surgery: a randomized controlled clinical trial.*

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Structured Abstract

Background:

Pulmonary resection surgery (PRS) requiring one-lung ventilation (OLV) is associated with hypoxemia and an exacerbated inflammatory response, contributing to postoperative complications. Strategies such as continuous positive airway pressure (CPAP) or apneic oxygenation (AO) applied to the non-dependent lung may mitigate these effects without or with minimal interference with surgical technique.

Methods:

This is a single-center, double-blinded, randomized controlled trial including 177 patients undergoing PRS. Patients will be randomized into three groups: (1) complete lung collapse (control), (2) apneic oxygenation at 3 L/min and (3) CPAP at 2 cmH_2O.

Randomization will follow a 1:1:1 allocation. Except of the anesthesiologist involved on surgery, all care providers, data collectors, and analysts will remain blinded. Predefined intraoperative ventilation protocols and postoperative care will be applied across groups. Blood and Bronchoalveolar lavage samples will be analyzed at specified intra- and postoperative time points.

Objectives:

The primary outcome is to assess whether AO or CPAP reduces the incidence of postoperative complications classified by the C-D scale. Secondary outcomes include the comparison between groups of hypoxemia episodes, lung and systemic inflammatory and oxidative stress biomarker levels, and surgeon-rated lung management.

Expected Results:

The study is expected to demonstrate that maintaining oxygenation in the non-dependent lung, even without positive pressure, may reduce episodes of hypoxemia, attenuate systemic and lung inflammation, and lower the incidence of postoperative complications, although CPAP will be less well tolerated by the surgeons.

Details of Trial Registration.

After we obtained the approval of the local ethics committee on January 23, 2025, we included the first patient in the study on January 29, 2025. We plan to spend around 25 months to include 177 patients and complete the trial January-March 2027. Protocol number ECAOI-22 version 2.2 December 2024. The study was

registered in Clinical Trials Information System (CTIS) on 10th October 2024 (EUCT NUMBER: 2024-517599-39, https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2024-517599-39-00).

Keywords (MeSH terms):

- One-Lung Ventilation
- Apneic Oxygenation
- Continuous Positive Airway Pressure
- Pulmonary Resection Surgery
- Inflammation
- Postoperative Complications

Introduction

Thoracic surgical interventions trigger a localized and subsequently systemic response aimed at initiating tissue repair, characterized by increased blood flow and vascular permeability (1). In addition to this systemic response, mechanical ventilation required during general anesthesia for these procedures can cause inflammatory lung injury (2–4). Pulmonary resection surgery (PRS) is considered a major operation associated with a substantial postoperative inflammatory response, more intense than that seen in abdominal surgery (5,6). This is primarily attributable to the need for one-lung ventilation (OLV) in most thoracic procedures to optimize surgical exposure.

OLV is associated with two well-known consequences: intraoperative hypoxemia and an exaggerated pulmonary inflammatory response, both of which may contribute to adverse perioperative outcomes (7–10). Hypoxemia remains one of the key challenges for anesthesiologists during OLV, with an incidence ranging from 4% to 10% (11). One common strategy to prevent or manage hypoxemia is the application of continuous positive airway pressure (CPAP) to the non-dependent (collapsed) lung, although this may interfere with the surgical field, depending on factors such as the level of applied pressure (12–15).

In recent years, apneic oxygenation (AO) has emerged as an alternative strategy — supplying oxygen to the non-dependent lung via a catheter without applying any positive pressure. Oxygen moves passively into the alveoli by pressure gradient from the proximal end of the non-dependent bronchial lumen (16–20). This

technique has been used to extend the safe apnea time during airway management in anesthetic induction (21), or to maintain oxygenation during procedures requiring limited respiratory movement (22,23) .

As for the inflammatory response, its intensity is known to correlate with the risk of postoperative complications following thoracic surgery(24). OLV initiates a significant inflammatory response in both the ventilated (dependent) and non-ventilated (non-dependent) lungs. While there is conflicting evidence regarding which lung suffers greater inflammatory insult(5,25), some authors have shown that avoiding complete collapse of the non-dependent lung — such as through the application of CPAP — may reduce lung and systemic inflammation, likely by mitigating ischemia-reperfusion injury that follows collapse and subsequent re-expansion(26).

We hypothesize that maintaining a continuous oxygen flow to the non-dependent lung — either with minimal pressure or no pressure — during OLV will reduce alveolar hypoxia in that lung and thereby attenuate ischemia-reperfusion injury, positively influencing postoperative outcomes. This approach may also decrease the incidence of intraoperative hypoxemia and allow the administration of lower oxygen concentrations to the dependent lung, further benefiting the patient's prognosis while minimally affecting the surgical technique.

The primary objective of this study is to compare postoperative complications classified by the Clavien-Dindo (C-D) scale, in patients undergoing OLV with the non-dependent lung managed via collapse, CPAP, or AO. Secondary objectives

include comparing lung and systemic inflammatory and oxidative stress biomarker levels, frequency of hypoxemic episodes, and surgeon satisfaction with intraoperative lung handling across the three groups.

Methods

Study Design

This is a single-center, doubled-blinded, randomized clinical trial conducted at a university hospital. Patients were randomly assigned into one of three study groups using computer-generated randomization, with allocation concealed in opaque envelopes:

1. Collapse (C) group: the non-dependent lung is left completely collapsed during OLV.

2. AO group: oxygen is delivered at 3 L/min with FiO_2 1 through the lumen of the double-lumen tube to the non-dependent lung during OLV.

3. CPAP group: continuous positive airway pressure at 2cm H_2O with FiO_2 1 is applied to the non-dependent lung during OLV.

All participants, surgical teams, and data analysts were blinded to group assignments throughout the study, except for the anesthesiologist responsible for intraoperative management.

This trial was approved by the hospital's Research and Ethics Committee on 23 January 2025, and all participants provided written informed consent prior to

inclusion. The study was registered in Clinical Trials Information System (CTIS) on 10th October 2024 (EUCT NUMBER: 2024-517599-39).

The trial will include patients over 18 years of age who are legally competent. Patients of both sexes scheduled to undergo PRS and requiring double-lumen tube (DLT) intubation at the Thoracic Surgery Department of Hospital Gregorio Marañón will be included. Participation is voluntary, and written informed consent will be obtained from all participants.

Exclusion criteria include pregnancy or breastfeeding, transfusion of blood products within the past 10 days, treatment with corticosteroids or immunosuppressants within 3 months before surgery, previous contralateral lung surgery, robotic surgery, pneumonectomy, presence of contralateral pulmonary bullae (≥ 1cm) or current participation in another clinical trial.

There is no patient or public involvement planned at the different trial stages, except for the reporting of potential adverse events by patients.

Intervention Plan

All patients enrolled in the study will follow standardized preoperative and postoperative protocols. These include antithrombotic and antibiotic prophylaxis, fasting for clear fluids until 2 hours before surgery, implementation of an enhanced recovery after surgery protocol when appropriate, and lung-protective ventilation strategies during both two-lung and OLV periods.

During the preoperative visit, a member of the research team will meet with each candidate to explain the study. If the patient agrees to participate, informed consent will be signed. No premedication or anxiolytics will be administered prior to surgery.

Participant timeline is shown in table 1.

Table 1. Participant Timeline

Visit	1	2	3	4	5	6	7	8
Day	-1	0	0	0	0	1	Alta	30
Place	Preanesthesia visit	Op room (BAS)	Op room (OLV 30)	Op room (TLV)	PACU	Ward	Ward	Office
Study Procedures								
Informed Consent	X							
Medical History	X							
Demographics	X							
Intervention								
Treatment			X	X				
Blood Samples								
Blood count Arterial blood gas Biochemistry Inflammatory markers	X X	 X X	X	X X	X	X X X X		
Bronchoalveolar Lavages								
Lung Op Lung Non Op		X X		X X				
Chest X-Ray								
Standing Lying	X				 X	X		X
Postoperative Events								
Postoperative Complications					X	X	X	X

Abbreviations: BAS: Basal, Lung Op: Operated Lung, Lung Non Op: Non operated Lung, OLV 30: One Lung Ventilation 30 minutes, Op room: Operating room, PACU: Post-Anethesia Care Unit, TLV: Two Lung Ventilation

Randomization

Patients will be randomized immediately before entering the operating room into one of three groups in a 1:1:1 ratio: the control group, the AO group, or the CPAP group. Randomization will be performed using EPIDAT 3.1 software prior to recruitment of the first patient. Randomization codes will be sealed in numbered envelopes. The attending anesthesiologist will open the envelope and prepare the designated oxygen delivery method accordingly.

To minimize bias, all other healthcare providers involved in the patient's care will remain blinded to group allocation. This includes the thoracic surgeon performing the procedure, the physician overseeing postoperative care in the post-anesthesia care unit (PACU) and inpatient ward, and the physician conducting follow-up at one-month post-surgery. Laboratory personnel analyzing biological samples will also be blinded to group assignment. Additionally, data entry personnel will not have access to group information; the allocation will be added to the database only immediately prior to statistical analysis.

Anesthetic Protocol

Induction and Monitoring

Upon arrival in the operating room and confirmation of informed consent, patients will undergo monitoring with non-invasive blood pressure, electrocardiogram, pulse oximetry, bispectral index, and neuromuscular relaxation monitoring. Anesthetic induction will be performed in all patients using lidocaine (1-1,5mg/kg), fentanyl (2–3 µg/kg), propofol (2–3 mg/kg), and rocuronium (0.6–1 mg/kg).

A DLT of appropriate size will then be inserted. Proper positioning of the DLT will be verified via auscultation and fiberoptic bronchoscopy. A radial artery catheter will be placed for continuous hemodynamic monitoring using the FloTrac®/Vigileo® system (Edwards Lifesciences, Irvine, CA, USA).

The patient will then be positioned in the lateral decubitus position, and a paravertebral catheter will be placed at the T5–T7 level on the ipsilateral side of the surgical procedure.

Maintenance

Anesthesia will be maintained with inhalational sevoflurane, titrated to achieve a bispectral index between 40 and 60. A bolus of 1.5% lidocaine (0.15 mL/kg, maximum 15 mL) will be administered via the paravertebral catheter prior to surgical incision, followed by a continuous infusion of 1.5% lidocaine at 0.15 mL/kg/h.

Additional doses of fentanyl and rocuronium will be administered as needed. Fluid therapy will be goal-directed. In cases of arterial hypotension, fluid boluses or vasopressors will be administered based on hemodynamic parameters and at the anesthesiologist's discretion.

Ventilatory Management

Two-Lung Ventilation (TLV): Following orotracheal intubation and prior to OLV, volume-controlled ventilation will be initiated with a tidal volume (TV) of 6–8 mL/kg of ideal body weight, a PEEP of 5 cmH_2O, and a respiratory rate adjusted to maintain

end-tidal CO_2 between 35–45 mmHg. The lowest FiO_2 required to maintain an oxygen saturation (SpO_2) of 96–98% will be used.

During OLV, a recruitment maneuver will be performed on the ventilated lung to determine optimal PEEP, following the iPROVE-OLV protocol for the individualized open-lung approach (iOLA) group (27). Lung-protective ventilation will be applied with a tidal volume of 4–6 mL/kg of ideal body weight. Respiratory rate and the inspiratory-to-expiratory ratio will be adjusted to allow permissive hypercapnia (pH ≥7,2) while avoiding air trapping. Efforts will be made to maintain a driving pressure (plateau pressure – PEEP) <15 cmHO. The minimum FiO_2 required to maintain a SpO_2 92-93% will be used.

If lung-protective ventilation or recruitment maneuvers cannot be applied (e.g., due to contraindications), this will be documented in the case report form (CRF), specifying the type of ventilation used and the reason for deviation of the protocol study.

Interventional Treatment

At the onset of OLV, patients in each study group will be managed as follows:

• **Control Group**: The lumen of the DLT corresponding to the operative lung will be disconnected, allowing the airway of the non-ventilated lung to be exposed to atmospheric pressure.

• **Apneic Oxygenation (AO) Group**: After cessation of ventilation to the non-dependent lung, oxygen will be administered via a catheter inserted through the

corresponding lumen of the DLT. The catheter tip will be positioned 1–2 cm below the carina within the appropriate bronchus and connected to a wall-mounted humidified oxygen source at a flow rate of 3 L/min. The DLT lumen used for apneic oxygenation must remain fully open to ensure free airflow through the bronchial lumen of the non-dependent lung Figure 1. The dependent lung will continue to be ventilated with the minimum FiO_2 required to maintain a SpO_2 of ≥92%.

• **CPAP Group:** Following the initiation of OLV, the lumen of the DLT corresponding to the operative lung will be disconnected. Once the pleural cavity is opened, a Mapleson circuit with a pressure control valve and a calibrated manometer will be connected. Airway pressure will be adjusted to maintain a CPAP of 2 cmH_2O, with an oxygen flow of 3–5 L/min, FiO2 1.

In both intervention groups, the assigned study technique (CPAP or apneic oxygenation) will be temporarily discontinued during lung parenchyma resection with the surgical stapler. This pause is intended to reduce the risk of intraoperative complications associated with airway pressure or gas flow at the time of stapling.

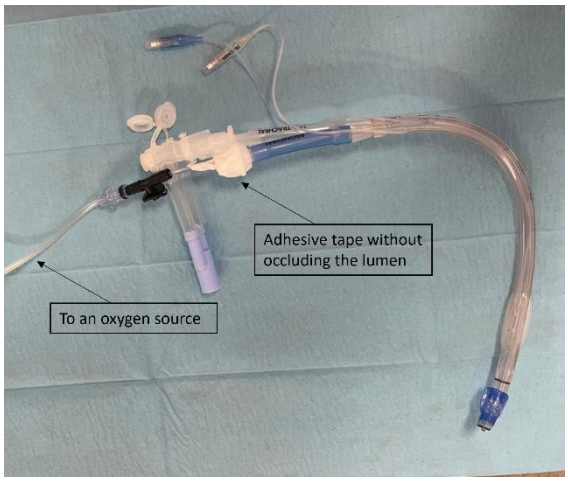


Figure 1. Apneic Oxygenation System

The approach to managing a hypoxemia episode on each group (defined as SpO_2 < 90% lasting more than 2 minutes) is presented in Table 2, as a step-by-step protocol.

Table 2. Management of hypoxemia episodes according to groups.

Control Group	AO Group	CPAP Group
Verification of correct DLT placement	Verification of correct DLT placement	Verification of correct DLT placement
Increase of FiO_2 to 1.0,	Increase of FiO_2 to 1.0,	Increase of FiO_2 to 1.0,
New lung recruitment maneuver	New lung recruitment maneuver	New lung recruitment maneuver
Initiation of CPAP in the non-dependent lung at 2 cm H_2O	Initiation of CPAP in the non-dependent lung at 2 cm H_2O	Intermittent TLV
Intermittent TLV	Intermittent TLV	

End of One-Lung Ventilation

At the end of the OLV period, TLV will be reestablished in all groups using a tidal volume of 6–8 mL of ideal body weight. A stepwise recruitment maneuver will be performed on TLV using a FiO_2 of 0.5, if the patient tolerates it and no contraindications are present. Following this, pre-OLV ventilatory settings will be restored.

At the conclusion of the surgical procedure, extubation will be attempted in the operating room at the anesthesiologist's discretion, followed by transfer to the PACU.

Postoperative Care

In the PACU, patients will be managed according to the institution's standard postoperative care protocol. Immediate postoperative assessment will include arterial blood gas analysis and chest radiography.

Analgesia will be maintained with continuous ropivacaine 0.2% infusion through the paravertebral catheter. Additional analgesics may include intravenous paracetamol 1 g every 8 hours, metamizole 2 g every 8 hours, or rescue boluses of 1-2 mg of morphine chloride if the visual analog scale pain score exceeds 4 points.

Patients will be followed until hospital discharge. At least one follow-up visit will be scheduled 30 days after surgery for the assessment of postoperative complications.

Variables to be collected in the study

Preoperative Data

Patient characteristics following PRO EDI Initiative are Recorded in Table 3 :

Table 3. Patient Characteristics following PRO EDI Initiative

Item	Description
Age	Median + Range
Sex	Male, Female, Intersex
Gender	Man, Woman, Other
Race/Ethnicity/ Ancestry	Latino, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other.
Socio-economic status	Assessed from Educational Level (Incomplete Primary Education or no schooling; Completed Lower Secondary; Some College, Vocational Training, or completed Upper Secondary; Completed University or College Bachelor's Degree, Postgraduate degree)
Geographic location	Country of residence

Anthropometry: weight, height, body mass index, Ideal body weight.

Preoperative clinical data: ASA physical status, personal medical history, toxic habits (e.g., smoking), respiratory infection within the last month, ARISCAT score (28), preoperative hemoglobin, preoperative pulmonary function tests (forced vital capacity [FVC], forced expiratory volume in the first second [FEV1], both in mL and percentage of predicted, carbon monoxide diffusion capacity, Tiffeneau index [FEV1/FVC]).

Intraoperative Data

We will register the type of surgery performed, duration of surgery, side of intervention, duration of OLV, surgeon's satisfaction score. Dosage of anesthetic agents used and ventilator parameters. Train-of-four ratio at extubation, fluidotherapy employed and use of vasoactive drugs.

During OLV, the following will be recorded every 15 minutes: SpO_2, FiO_2 and PEEP of the dependent lung; the number of hypoxemic episodes and lowest registered SpO_2, as well as the methods used to manage each hypoxemic episode.

Additionally, the following hemodynamic and respiratory variables will be collected at three time points: 1) Lateral decubitus position during TLV, 2) 30 minutes after initiating OLV, and 3) 15 minutes after resuming TLV:

o Hemodynamics: Mean arterial pressure, heart rate, cardiac index, stroke volume index, stroke volume variation, pulse pressure variation.

o Respiratory: Tidal volume, respiratory rate, minute volume, airway pressures (peak, plateau, PEEP, mean, driving pressure), lung compliance, FiO_2, $EtCO_2$, SpO_2.

At the end of surgery, the surgeon will be asked to rate their satisfaction with the quality of surgical lung management. The response will be recorded on a modified 5-point Likert scale (Figure 2):

1. Surgery impossible. Oxygen administration method must be changed;
2. Technique extremely difficult. No need to change oxygen administration;
3. Significantly more difficult than usual;

4. Slightly more difficult than usual;
5. Similar to usual. I did not notice any difference.



Figure 2. Visual Likert Scale

Blood Samples

Arterial blood samples will be drawn in the lateral decubitus position during TLV, 15 minutes after OLV initiation, and 15 minutes after TLV resumption. These samples will be analyzed for:

• Blood gases: PaO_2, $PaCO_2$, pH, HCO_3^-. Indices of pulmonary function, including the PaO_2/FiO_2 ratio, the alveolar–arterial oxygen gradient or the effective shunt fraction (29).

• Biomarkers (measured at the above time points + 24 hours postoperatively): NLRP3 inflammasome components: IL-1β, IL-18, caspase-1, Apoptosis-Associated Speck-like protein (ASC). Proinflammatory cytokines: IL-6, IL-8, TNF-α. Endogenous NLRP3 regulators. Mitochondrial biogenesis markers: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α), Mitofusin 1 y 2, AMP-activated protein kinase (AMPK), Nuclear Respiratory Factor 1 (TFAM). Oxidative stress markers: Superoxide Dismutase (SOD), Malondialdehyde (MDA), Myeloperoxidase (MPO), Cysteine Protease (CP), Reactive Oxygen Species (ROS) index (plasma thiol loss, carbonyl groups).

Sample handling: 9 mL blood samples will be centrifuged (400 ×g, 15 min), and supernatants stored at −20°C for analysis.

Bronchoalveolar Lavage Samples

Bronchoalveolar lavage will be performed before OLV initiation and 15 minutes after resuming TLV. A 4.5-mm fiberoptic bronchoscope will be advanced and wedged into a segmental bronchus of the left lower lobe or right middle/lower lobe, followed by instillation of 20 mL of 0.9% saline. The collected samples will be filtered through sterile gauze, centrifuged (400 ×g, 4°C, 15 minutes), and the supernatants stored at −20°C for subsequent analysis. These samples will be analyzed for the biomarkers described above at the Complutense University of Madrid Biochemical Deparment.

Postoperative Course

All postoperative complications within 30 days after surgery will be recorded and graded using the modified C-D scale for thoracic surgery (TM&M) (30–32) (Table 4). Postoperative pulmonary complications (PPCs), surgical complications and complications related to other organs will be defined following the TM&M definitions (31,32).

Table 4. Modified Clavien-Dindo scale for thoracic surgery.

Grade	Definition
Complication	Any deviation from the normal postoperative course.
Minor	
Grade I	Any complication without need for pharmacologic treatment or other intervention.
Grade II	Any complication that requires pharmacologic treatment or minor intervention only.
Major	
Grade III	Any complication that requires surgical, radiologic, endoscopic intervention, or multitherapy.
Grade IIIa	Intervention does not require general anesthesia.
Grade IIIb	Intervention requires general anesthesia.
Grade IV	Any complication requiring intensive care unit management and life support.
Grade IVa	Single organ dysfunction.
Grace IVb	Multiorgan dysfunction.
Mortality	
Grade V	Any complication leading to the death of the patient.

Also, we will record: length of stay at PACU and hospital, the need for reoperation, and unplanned readmission to PACU/hospital within 30 days

Study Data Collection and Management

All the intraoperative clinical variables described will be recorded in the CRF by the anesthesiologist responsible for the surgery. The thoracic surgeon responsible for the surgery will be asked to rate the satisfaction with the surgical management. Additionally, data will be documented in the electronic medical record (EMR).

Anesthesiologists and thoracic surgeons evaluating the postoperative course, not related with the intraoperative management, will collect preoperative and postoperative first 24h clinical and analytical variables, and intraoperative analytical variables.

Two separate investigator teams (anesthesiologists and thoracic surgeons) will independently assess postoperative complications and final (C-D) scale one month after surgery. The definition of PPC will be supported by pneumologists. In case of disagreement, a joint meeting will be held to reach a consensus. Data will be obtained via EMR review and, if necessary, patient interviews. Investigators will be blinded to patient group allocation.

Authorship will be determined according to the recommendations of the ICMJE guidelines (33).

Full protocol will be published in Trials. All patient data and the statistical analysis will be submitted to the selected journal for publication of the results, and will be publicly accessible upon request.

CRF Handling and Data Entry

The CRF will include all variables described at each clinical stage. At hospital discharge, the CRF will be stored in a locked cabinet in the anesthesiology department. 30-day postoperative data will be added to the CRF one month after surgery. Once the CRF is completed, data will be entered into SPSS.

In order to verify protocol compliance and error detection, every data included in the CRF will be audited weekly by an external clinical research organization (CRO), selected through a public tender process. In addition, this organization was responsible for performing the administrative procedures required for submission of the trial to the ethics committee and the European Medicines Agency via CTIS, as well as for ensuring compliance with all applicable legal requirements and regulations governing clinical drug trials. It will also be responsible for ongoing administrative follow-up, monitoring of potential adverse events, responding to regulatory queries, and submitting any necessary protocol amendments.

Patients will be withdrawn from the study if: Protocol procedures cannot be followed for medical reasons, intraoperative blood product transfusion is required or an adverse clinical event warrants withdrawal per investigator judgment, or the patient voluntarily withdraws consent.

Statistical analysis

The sample size estimation was based on the primary endpoint: the difference in the distribution of C-D scale (I-V grades) across the three trial groups, which will indicate the severity of postoperative complication.

A simulation-based approach using the Kruskal-Wallis test in R 4.4.2 (R Foundation for Statistical Computing) generated 1,000 datasets per sample size for three groups with predefined complication distributions, and statistical power was assessed iteratively by increasing the sample size until achieving 80% power (1-β). The control group probability distributions were based on previous studies, with major complications (CD≥III) reported in 11%-16.5% of lobectomy patients (31,34). A sample of ≥56 patients per group (α=0.05, β=0.20) was required to detect ≥1-unit difference in the severity distribution between groups, totalling 177 patients, accounting for 5% dropout.

Continuous variables will be reported as mean (standard deviation) or median (interquartile range), depending on their distribution. Normality will be evaluated using the Kolmogorov–Smirnov test. Group comparisons will be made using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test as appropriate. The ordinal distribution of the C-D scale will also be analyzed with the Kruskal–Wallis test.

To assess longitudinal changes in biomarkers, a linear mixed-effects model will be employed, applying log transformation when necessary to satisfy model assumptions. In cases where baseline cytokine levels differ significantly between groups, post hoc analyses will focus on the rate of change rather than absolute values at follow-up time points.

Categorical variables will be expressed as counts and percentages, and compared using Pearson's Chi-square test or Fisher's exact test as appropriate. Bonferroni

adjustment will be applied to correct for multiple comparisons. All statistical analyses will be performed with SPSS version 28.0. All randomized participants with either observed or imputed outcome data will be included in the primary and secondary analysis. The analysis will follow the intention-to-treat principle, and statistical significance will be defined as a p-value < 0.05.

An interim analysis is scheduled to be conducted with a cohort comprising half of the enrolled patients for the purpose of evaluating the study's safety. Adverse events will be systematically analyzed within each treatment group; should there be a statistically significant increase in adverse events in the intervention groups compared to the control group, the study will be terminated. Access to this analysis will be granted to the study's principal investigator and the CRO.

Access to data and dissemination policy

The study data will be kept in a locked cupboard, and only members of the research team and the external CRO will be able to access the database. The results of the study will be made public through publication in scientific journals and conferences related to anesthesia in thoracic surgery.

Discussion

This study aims to address the two primary concerns of the anesthesiologist in this type of surgery. First, the improvement of arterial oxygenation through a device that is effective and does not interfere with the surgeon’s work; and second, the incorporation of a novel intraoperative lung-protective strategy to reduce the postoperative pulmonary injury that, to some extent, inevitably occurs following

this type of procedure. Traditionally, it has been assumed that pulmonary injury occurs primarily in the dependent lung, and lung-protective strategies have largely focused on minimizing damage to this lung. However, emerging scientific evidence suggests that the non-dependent lung can also contribute significantly to lung injury, albeit through different mechanisms. For example, De la Gala et al. (5) demonstrated that inflammatory responses were similar in both lungs during OLV. Additional studies have further challenged the notion that the dependent lung is the sole or primary site of injury. Moreover, Sánchez Pedrosa et al, in a porcine experimental model, investigated the impact of surgical manipulation on lung injury (35), reinforcing the concept that intraoperative handling of the non-dependent lung may also play a significant role.

On the other hand, it has been observed that oxidative stress-related injury occurs in the non-ventilated lung, which is associated with the reduced pulmonary blood flow resulting from hypoxic pulmonary vasoconstriction and the subsequent reperfusion following the end of OLV. This ischemia/reperfusion phenomenon induces significant oxidative stress (36), which is more pronounced in patients with lung cancer due to their increased oxidative burden and reduced antioxidant capacity (2). Re-expansion of the non-ventilated lung after OLV has been shown to trigger the release of oxygen free radicals (2,37–39) likely related to ischemia/reperfusion injury, although the impact of this process on postoperative outcomes has not yet been thoroughly investigated. Oxidative stress injury is well recognized in the pathophysiology of acute respiratory distress syndrome (40) and a positive association between oxidative stress and respiratory failure has been

documented in patients undergoing OLV (39). Both experimental and clinical studies have demonstrated that prolonged lung collapse leads to increased oxidative stress levels in bronchoalveolar lavage fluid and blood samples (2–4)

Patients receiving AO may experience a more favorable postoperative course if this intervention is shown to reduce inflammatory damage and the generation of free radicals—key factors involved in the pathogenesis of acute respiratory distress syndrome, the leading complication in patients undergoing thoracic surgery. Additionally, this study will evaluate whether the systematic use of low-pressure CPAP in the operated lung provides equal or greater benefits than AO, and to what extent it interferes with the surgical technique.

If the hypothesis that CPAP or AO can reduce the incidence of postoperative complications with minimal interference in surgery proves true, these strategies could become valuable additions to the anesthesiologist's arsenal of prophylactic measures aimed at improving postoperative outcomes. Until now, such measures have primarily focused on protecting the dependent lung; therefore, incorporating interventions targeting the non-dependent lung could lead to a substantial reduction in the overall incidence of postoperative complications. Furthermore, the clinical implementation of the findings would be immediate, as no current studies have been designed with postoperative complications as their primary outcome.

The C-D scale will be used to assess the relevance of postoperative complications, as it emphasizes the clinical impact of each deviation from the expected postoperative course rather than simply defining complications.

AO has been shown to reduce the incidence of hypoxemia during pulmonary resection surgery (17,18), and it may also decrease the number of interventions required by the anesthesiologist to correct hypoxemia, thereby facilitating the surgical technique. Recently, AO has also been associated with reduced production of inflammatory markers and decreased oxidative damage related to OLV in esophageal surgery (41). However, to our knowledge, no studies have evaluated the impact of apneic oxygenation during pulmonary surgery with respect to inflammatory response, oxidative stress, ischemia-reperfusion injury, and postoperative complications.

CPAP is commonly used as a rescue strategy to treat intraoperative hypoxemia during OLV. Although initial recommendations suggested applying CPAP at pressures of 5–10 cm H_2O (13) subsequent studies highlighted the surgical difficulties associated with these higher pressures. In recent years, lower pressure settings have been advocated, and more recently, Boisen et al. demonstrated that applying CPAP at 2 cm H_2O effectively improves arterial oxygenation during OLV without interfering with surgical manipulation (14,15,42). However, current evidence remains limited. Additionally, during esophageal surgery, the application of CPAP to the non-dependent lung was shown to reduce inflammatory markers in both the ventilated and non-ventilated lungs (26).

In contrast, the use of apneic oxygenation remains scarce, and there is very limited high-quality data available (22,23,41). Moreover, the potential prophylactic role of either technique in attenuating the pulmonary/systemic inflammatory response and improving the postoperative course has been poorly described. While current

molecular mechanisms focus on oxidative stress-related damage, this study proposes exploring other, previously uninvestigated biochemical aspects, such as the role of inflammasomes.

An important limitation of this study is that it will be conducted at a single center. Furthermore, pulmonary inflammatory biomarkers will only be assessed intraoperatively, while systemic markers will be analyzed up to 18 hours post-surgery. Nonetheless, in a previous study, we observed an association between PPCs and inflammatory markers within the same time frame (24). Another potential limitation is the fact that the anesthesiologist performing the procedure will also be responsible for administering the assigned treatment and recording intraoperative data, thus being unblinded. Patients undergoing robotic surgery will not be included in the trial, as we consider that certain factors — such as the specific surgical technique involving capnothorax or the prolonged operative time — may introduce bias into the results. Additionally, technical difficulties faced by the surgeons — such as the presence of residual gas in the operated lung — may impact the duration of surgery or lead to postoperative surgical complications, which in turn could influence the C-D score.

This study aims to elucidate the role of oxygen therapy — administered with or without pressure — to the operated lung in potentially attenuating the systemic inflammatory response and oxidative damage, and to determine whether these effects correlate with improved postoperative course. Additionally, the study will assess whether oxygen delivery to the operated lung enhances oxygenation

parameters, and evaluate the clinical relevance of such improvements for patient outcomes.

Trial status

After we obtained the approval of the local ethics committee on January 23, 2025, we included the first patient in the study on January 29, 2025. We plan to spend around 25 months to include 177 patients and complete the trial January-March 2027. Protocol number ECAOI-22 version 2.2 December 2024. The study was registered in Clinical Trials Information System (CTIS) on 10th October 2024 (EUCT NUMBER: 2024-517599-39).

Abbreviations

AO: Apneic Oxygenation, C-D: Clavien-Dindo, CPAP: continuous positive airway pressure, CRF: case report form, OLV: One Lung Ventilation, PACU: Post-anesthesia care unit, PPC: Postoperative pulmonary complications, PRS: pulmonary resection surgery, TLV: Two Lung Ventilation.

Declarations

Acknowledgements

No applicable.

Authors' contributions

DM, FDG, IG and CS provided the original idea. DM, FDG, IG, CS, and EV contributed to the study concept and design. DM, FDG, IG, CS and EV wrote the manuscript. EV

and LR processed and analyzed the biological samples. The other authors participated in patient recruitment and data collection. All authors read and approved the final manuscript.

Funding

Instituto de Salud Carlos III. Ministerio de Sanidad España. Grant PI23/00386 (121.250€).

Availability of data and material

All data and supplementary material will be available upon request.

Ethics approval and consent to participate

This clinical study protocol has been approved by the Hospital Gregorio Marañon Ethics Committee on January, 23 2025. One of the anesthesiologists involved in the study will obtain informed and signed consent from patients when recruiting before the surgery. Consent will also be obtained for the analysis of data and samples in ancillary studies. The patients can withdraw from the trial at any time. The law requires carrying civil liability insurance that covers possible damages that may result for patients included in the study and guaranteeing compliance with data protection laws.

If the protocol requires modification, the ethics committee will be notified first, and the necessary reports will be submitted via CTIS. Once the modification is authorized, the parties will be informed during an in-person meeting and in writing via institutional email.

Consent for publication

All authors agree to the submission to Trials and publishing of this article.

Competing interests

The authors declare that they have no competing interests.

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