# RESEARCH PROTOCOL

**Rationale and study design for an Individualized PeriopeRative Open lung Ventilatory stratEgy in patients submitted to One Lung Ventilation (iPROVE-OLV): study protocol for an international multicenter randomized controlled trial.**

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## 1. Abbreviations

**ARDS**, Acute respiratory distress syndrome; **ARM**, Alveolar recruitment maneuvers; **ASA**, American Society of Anesthesiologists; **BIS**, Bispectral analysis; **BMI,** Body mass index; **Bpm**, Breaths per minute; **CI**, Confidence interval; **COPD**, Chronic obstructive pulmonary disease; **CPAP**, Continuous positive airway pressure; $\mathbf{C_{dyn}}$, Dynamic compliance of the respiratory system; **CT**, Computed tomography; **DP**: driving pressure; **ECG**, Electrocardiogram; **EPAP**, Expiratory positive airway pressure; $\mathbf{EtCO_2}$, End-tidal carbon dioxide partial pressure; **EVA**, Visual analog pain scale (*echelle visuelle analogique* EVA); $\mathbf{FiO_2}$, Inspiratory oxygen fraction; **GCS**, Glasgow Coma Score; **HFNC**: high-flow nasal cannula; **HR**, Heart rate; **ICU**, Intensive care unit; **I:E**, Inspiratory-to-expiratory ratio; **IPAP**, Inspiratory positive airway pressure; **iPROVE**, Individualized perioperative open lung ft hetor strategy; **LOS**, Length of stay; **LPV:** lung protective ventilation; **MAP**, Mean arterial pressure; **MV**, Mechanical ventilation; **NIV**, Noninvasive ventilation; **OLA**: open-lung approach; **OLV**: one-lung ventilation; $\mathbf{PaCO_2}$, Partial pressure of carbon dioxide; **PACU**, Postoperative care unit; $\mathbf{P_{aw}}$, Peak airway pressure; **PBW**, Predicted body weight; **PCV**, Pressure control ventilation; **PEEP**, Positive end-expiratory pressure; **PPCs**, Postoperative pulmonary complications; $\mathbf{P_{plat}}$, Plateau pressure; **PONV**, Postoperative nausea and vomiting; **PPV**, Pulse pressure variation; $\mathbf{R_{aw}}$, Respiratory system resistance; **RR**, Respiratory rate; **SBP**, Systolic blood pressure; **SOFA**, Sequential Organ Failure Assessment; $\mathbf{SpO_2}$, Peripheral capillary oxygen saturation; **SSI**, Surgical site infection; **STD**: standard; **SVV**, Stroke volume variation; **TOF**, Train of four; **VCV**, Volume control ventilation; **VILI,** Ventilator-induced lung injury; **VT**, Tidal volume.

## 2. Abstract

**Introduction:** Postoperative pulmonary complications are a common problem in at-risk surgical patients despite that lung protective ventilation (LPV) has decreased its prevalence. These complications are associated with worse prognosis, and an increase in hospital length-of-stay (LOS) and mortality. Some ft hetor strategies, such as intraoperative open-lung approach (OLA) or high-flow nasal cannula (HFNC) in the postoperative period have shown to decrease postoperative pulmonary complications. However, no studies have evaluated these strategies when applied together.

**Hypothesis:** A perioperative ft hetor management including an intraoperative OLA (using low tidal volume, alveolar recruitment maneuvers, individualized positive end-expiratory pressure) followed by individually apply postoperative HFNC will decrease postoperative complications, unplanned readmission, ICU and hospital LOS, and mortality compared to a standardized LPV in high-risk surgical patients.

**Methodology:** To examine our hypothesis, we will perform an international multicenter randomized, controlled clinical trial in 1380 patients scheduled to thoracic surgery admitted in a network of Spanish hospitals. After obtaining the informed consent, patients meeting inclusion criteria will be randomized into two groups: 1) iOLA-iHFNC: perioperative open-lung approach (n=690); 2) STD-O2: intra- and postoperative standard ventilation (n=690). We will analyze postoperative complications, unplanned readmission, and ICU and hospital LOS and mortality in both groups,

**Expected Results**: If our hypothesis is supported, the intraoperatively application of OLA followed by an individual indication of HFNC in the post-operative period will reduce pulmonary complication and LOS in high-risk surgical patients.

## 3. Introduction

Pulmonary resection surgery has an estimated risk of postoperative pulmonary complications (PPCs) of 30% [1] and an incidence of mild respiratory distress syndrome (ARDS) in the postoperative period between 4 and 15% depending on the type of pulmonary resection [2]. This incidence has a very significant impact on costs in health systems [3]. The thoracotomy is also a cause of perioperative mortality. Postoperatively, the ventilator induced lung injury (VILI) and ARDS, often a consequence of VILI, are the main causes of morbidity and mortality after lung resection surgery [4].

Numerous studies performed in patients with healthy lungs have shown that mechanical ventilation (MV) by itself can promote PPCs, which worsens the patient's prognosis and might increase mortality [5-7]. The main mechanisms of lung injury and ARDS related to MV are volutrauma and atelectrauma [5]. Even for short periods of time, volutrauma and atelectrauma produce an inflammatory response that favors the appearance of VILI [6,8] and the appearance of systemic organic dysfunction [9]. The latest evidence points to the driving pressure, calculated as the difference between the plateau pressure minus the positive end-expiratory pressure (Pplat-PEEP), as the most important independent risk factor related to the appearance of PPCs. The appearance of these PPCs (atelectasis, hypoxemia, pneumonia and lung injury) increase the need and the days of MV in the postoperative period, increases the unscheduled readmissions in the ICU and lengthens the stay in the ICU and in the hospital [10 -14].

Lung protective ventilation with low tidal volume (VT) and moderate-to-high levels of PEEP has shown to reduce PPCs even when applied in the operating room for short periods of time in patients with healthy lungs [15-16]. It is established that low (VT of 5-6 ml/kg predicted body weight) –both in one and two-lung ventilation- decreases the appearance of PPCs due to the attenuation of volutrauma [17,18]. However, there is some controversy about the benefits of PEEP in reducing PPCs [19]. During OLV PEEP mitigates atelectrauma and seems to decrease lung injury, and has also been shown to be necessary during the intraoperative period to maintain the patient in optimal oxygenation and ventilation conditions [20-24]. But, on one hand, the level of adequate PEEP during OLV has always been in question and it has been preferred to use "moderate" levels in order to minimize undesirable effects, mainly the appearance of intrinsic PEEP and alveolar overdistension [25, 26]. On the other hand, currently there are no studies that have described the level of optimal PEEP during OLV for the reduction of PPCs.

Recently, our group has shown that the appropriate way to adjust the level of PEEP in terms of oxygenation and respiratory mechanics is by means of an individualized adjustment looking for the level of PEEP that is associated with the best compliance (Cdyn) within an open lung approach (OLA), ergo, after an alveolar recruitment maneuver [27]. In addition, this strategy would achieve

the lowest value of driving pressure at a given VT, potentially increasing its protective value. To all this we must add that recent evidence suggests that to establish an adequate protective strategy it is needed a combination of a low VT and an adequate level of PEEP [18].

Finally, during the immediate postoperative period there is an increased risk of respiratory dysfunction, which increases the risk of developing other PPCs due to different factors related to the patient, the surgery and the general anesthesia, such as the presence of atelectasis produced during the intraoperative period, postoperative pain or the residual effects of general anesthesia. That is why a ft hetor support during this initial postoperative phase, such as the use of high-flow nasal oxygen therapy (HFNC), can be beneficial. The HFNC partially supplements the respiratory function decreasing the respiratory work, since it maintains functional residual capacity and washes carbon dioxide [28]. Although the benefits of postoperative ft hetor support to treat postoperative respiratory failure in thoracic surgery are clear [29-31], the benefits of the HFNC as a preventive strategy are not so evident [32,33].

## 4. Rationale.

First af all we believe that a pragmatic and standardized adjustment of PEEP, which is currently the common practice, is erroneous since a level of PEEP less or equal to the alveolar closing pressure will favor the reappearance of alveolar collapse after the recruitment maneuver. And if it is greater than what its needed, it will increase the risk of overdistention. Both factors are recognized as determinants of the deterioration of lung function during the intraoperative period and increase the risk of postoperative lung injury.

In second place, although it seems that the most important independent risk factor for PPCs is the driving pressure, today there are no prospective randomized controlled studies comparing different ft hetor strategies whose aim is to reduce this pressure. Results of different studies performed by our team, in the same population or on patients with similar ft hetor characteristics, suggest that the individualized OLA decreases the driving pressure for a given VT, potentially increasing the protective effect of this strategy.

Finally, the HFNC during the immediate postoperative period could reduce PPCs, this is not clearly demonstrated in the literature and this strategy has never been individually applied, and in combination with an intraoperative OLA.

## 5. Hypothesis and Objectives

### Hypothesis

The conceptual hypothesis of the study is the comparison of the standard and established perioperative ventilatory management to patients undergoing thoracic surgery requiring one-lung ventilation versus a strategy of individualized perioperative open-lung ventilator approach consisting in the joint use of low VT, realization of alveolar recruitment maneuvers, individualized adjustment of the PEEP and individualization of the ft hetor support in the immediate postoperative period will reduce postoperative pulmonary complications and with it, the unscheduled re-entry and length of stay in the critical care unit, the hospital length-of-stay and the overall mortality of these patients.

The operative hypothesis has been formulated as a null hypothesis of no differences in postoperative pulmonary complications between individualized and standardized ft hetor management in moderate-to-high risk patients.

**Primary objective:**

To evaluate the efficacy of the experimental ventilatory strategy to reduce postoperative pulmonary complications during the first 7 days after surgery, compared with the conventional ventilatory management.

**Secondary objectives:**

To evaluate the efficacy of the experimental ventilatory strategy to reduce postoperative pulmonary and/or systemic complications, unscheduled ICU and Hospital admissions, ICU and Hospital length of stay during the first 30 days after surgery, compared with the conventional ventilatory management.

**6. In summary,**

**6.1. Clinical problem and magnitude of the problem.**

Mechanical ventilation by itself, in healthy lungs, can promote PPCs. The literature shows that ventilation with high VT and low PEEP favors the appearance of PPCs. The use of lung protective ventilation with lower VT and adequate PEEP could reduce PPCs, the need for postoperative ventilator support, unplanned ICU and hospital readmissions and ICU and hospital length of stay. Likewise, during the immediate postoperative period there is an increased risk of developing pulmonary dysfunction due to different causes, both anesthetic and surgical. Some studies have shown that the ventilatory support during this phase could reduce postoperative complications.

Although lung protective ventilation has decreased the prevalence of PPCs, its prevalence in patients undergoing thoracic surgery is around 20-30%. The appearance of complications worsens the patient's prognosis and increases the consumption of health resources.

**6.2. Action proposal.**

Different ventilatory strategies such as the use of a physiological low-VT, recruitment maneuvers, individualized PEEP and HFNC in the postoperative period, which are not widely used in routine clinical practice, have been shown to reduce the incidence of postoperative complications. However, there is no prospective, controlled and randomized clinical study that demonstrates that the use of a perioperative open lung strategy consisting of performing recruitment maneuvers plus individualized PEEP adjustment during the intraoperative period along with the postoperative individualized indication of HFNC decrease postoperative pulmonary complications with respect to a standardized ventilation strategy.

In this study, the effectiveness of the application of a perioperative open lung strategy will be evaluated. If it were shown that it reduces postoperative pulmonary complications, it would represent a notable advance in the clinical management of these patients. In addition, a reduction in these complications would reduce the use of healthcare resources.

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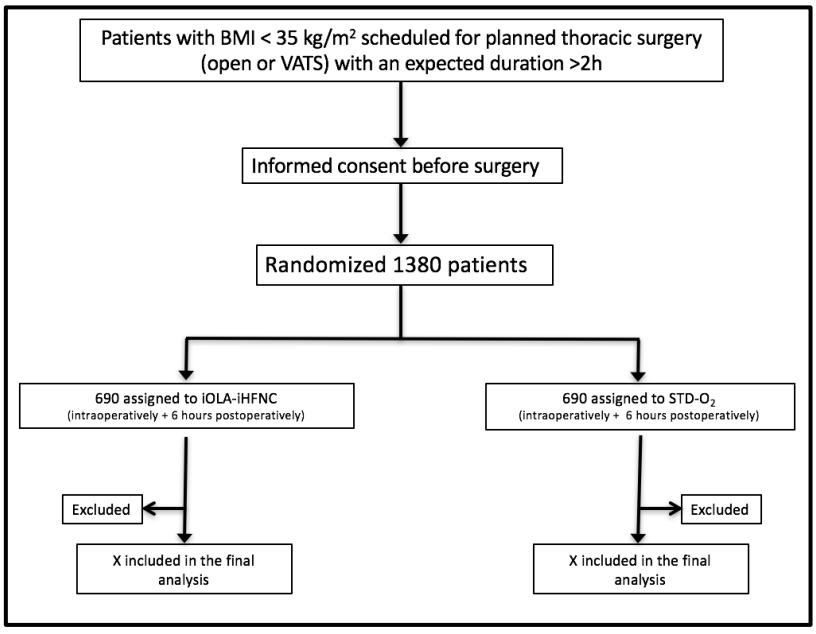
## 8. Methods.

### 8.1 Study design

The trial has been designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council relating to human rights and biomedicine, and the Universal Declaration of UNESCO on the human genome and human rights, and with the requirements established by Spanish legislation in the field of biomedical research, the protection of personal data, and bioethics, which was classified by the Spanish Agency of Drugs and Medical Devices as a clinical randomized study without drugs on september 7th, 2017 and registered on 2017 at http://www.clinicaltrials.gov with identification no. NCT03182062. Approval of the final protocol by the local committee at each participation center will be required before patient enrollment.

International multicenter, controlled, not masked, clinical trial with random assignment of patients to two parallel groups of ventilatory management:

**Figure 1. CONSORT flowchart**



1. **Group STD-O2:**

After initiating selective pulmonary ventilation, all patients will receive lung protective ventilation with a VT of 5-6 ml/kg of ideal body weight, PEEP of 4 $cmH_2O$ and $FIO_2$ of 0.8. During the the first 6 postoperative hours patients will be oxygenated with the minimum $FIO_2$ to maintain a $SpO_2$ ≥92%.

2. **Group iOLA-iHFNC:**

After initiating selective pulmonary ventilation, an alveolar recruitment maneuver followed by a PEEP titration trial will be performed to all patients. Patients included in this group will be ventilated intraoperatively with a VT of 5-6 ml/kg of ideal body weight, open-lung PEEP and with an $FIO_2$ of 0.8. After extubation, approximately 15 minutes once entered into the post-anesthesia care unit (PACU), an Air-Test (which consists in breathing at $FIO_2$ 0.21 for 5 minutes) will be performed. During the first 6 postoperative hours [in the case of negative Air-Test ($SpO_2$ ≥97%)] the patient will be oxygenated with the minimum $FIO_2$ to maintain an $SpO_2$ ≥92%. In the case of positive Air-Test ($SpO_2$ ≤96%), high-flow oxygen therapy (HFNC) with a flow rate of ≥ 50 lpm will be indicated with the minimum $FIO_2$ to maintain a $SpO_2$ ≥92%.

**8.2 Study population**

The study population consist of adult male and female ≥18 years old, who are scheduled for an open or video-assisted thoracic surgery with selective pulmonary ventilation and an expected mechanical ventilation time of ≥2 hours (surgery time of 2h). Patients who meet all of the following inclusion criteria and none of the exclusion criteria will be consecutively included:

*Exclusion criteria:* 1) Pregnancy or breast-feeding, 2) moderate or severe ARDS defined as $PaO_2/FiO_2$ < 200 mmHg, 3) diagnosis of heart failure defined as: IC <2.5 ml/min/$m^2$ and/or inotropic support before surgery and/or or suspicion of heart failure according to clinical signs (hypotension, oliguria, pulmonary edema) together with NT-proBNP >13 pg/ml, 4) diagnosis or suspicion of intracranial hypertension (>15 mmHg), 5) mechanical ventilation in the last 15 days (including CPAP), 6) presence of pneumothorax or giant bullae on a chest radiograph or computed tomography (CT), 7) patients with chronic obstructive pulmonary disease (COPD) requiring oxygen or CPAP, and patients participating in another interventional study with similar primary outcomes, 8) Previous lung resection.

### 8.3 Method of randomization and bias minimization

Informed consent will be obtained from each participant before enrollment in the study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be consecutively included and randomized into one of the two study arms (Figure 1).

The patients will be randomized online via the website http://iprove.incliva.es using the Mersenne Twister algorithm with an allocation rate of 1:1.

Blinding: At least two investigators are required in each participating center, because the study characteristics do not allow the blinding of investigators in the operating and postoperative room, so data acquired in these sites will not be blinded. After 24 h, all data will be acquired by the second investigator who will be blinded to the randomization arm.

### 8.4 Study variables

The primary outcome of the iPROVE trial is a composite of pulmonary complications experienced by the study population in the first 7 days after surgery as discussed below.

1. Atelectasis that requires bronchoscopy. The atelectasis is defined as chest X-ray images suggesting lung opacities with a shift in the mediastinum, hilum, or hemidiaphragm toward the affected area and compensatory over-inflation in the adjacent non-atelectatic lung.
2. Severe respiratory failure: Hypoxemia (defined as $SpO_2$ of 92% or less with 0.21 $FiO_2$ or $SpO_2$ of 95% or less with 0.5 $FiO_2$) requiring ventilatory support
3. Contralateral pneumothorax: air in the pleural space and the mediastinum is shifted to the opposite side (a thorax radiography will be performed in suspected cases of auscultation hoarseness).
4. Early extubation failure or requirements of reintubation
5. ARDS: according to the Berlin definition
6. Suspicion of pulmonary infection or pneumonia: Treatment with ATB or/and the presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest radiograph plus at least two of the following criteria: (a) leukocytosis with >12,000 WBC/$mm^3$ or leukopenia with <4000 WBC/$mm^3$, (b) fever >38.5° C or hypothermia <36°C, and (c) increased secretions with purulent sputum and a positive bronchial aspirate.
7. Bronchopleural fistula
8. Pleural empyema with or without surgical reintervention

The secondary outcomes are the composite of postoperative pulmonary complications over the first 30 post-surgical days. Other secondary outcomes are:

Other pulmonary complications:

1. Atelectasis without bronchoscopy
2. Hypoxemia without requirements of supplementary oxygen or ventilator support.
3. Contralateral pleural effusion: chest x-ray with the presence of costophrenic angle blunting, displacement of adjacent anatomical structures, and blunting of the hemidiaphragmatic silhouette in the supine position
4. Bronchospasm: presence of expiratory wheezing treated with bronchodilators.
5. Aspiration pneumonitis: respiratory failure after the inhalation of regurgitated contents.
6. Pulmonary thromboembolism
7. COPD reagudization.
8. Hemothorax with or without surgical reintervention or transfusion.

Systemic complications:

1. Cardiac ischemia
2. New atrial fibrillation
3. Sepsis or septic shock
4. Acute kidney failure
5. Surgical site infection
6. Other infections (catheter, urinary tract…)

Other secondary outcomes are:

1. Claven-Dildo classification
2. ICU and hospital length of stay
3. ICU and hospital readmission in the first 30 days after surgery
4. Mortality within the first 30 days

The primary and secondary data outcomes will be taken at 1, 2, 5, 7, and 30 days after surgery. Plasma samples will be taken preoperatively and at 2 days after surgery. If the patient is not extubated in the operating room, the first four data time points will be taken from the time of extubation.

### 8.5 Other follow-up variables

Baseline variables will be recorded preoperatively and are age, sex, height, weight, body mass index, American Society of Anesthesiologists (ASA) physical status, Charlson comorbidity index, preoperative pulmonary function test, sequential organ failure assessment (SOFA) score, ARISCAT risk score, type of intervention, and medical history.

Intraoperative parameters recorded at three different time points (post-induction, 60 min after induction, and pre-extubation) will be: arterial blood gases, $SpO_2$, $FiO_2$, respiratory variables [VT, PEEP, $P_{aw}$, $P_{plat}$, $C_{rs}$, respiratory system resistance ($R_{aw}$), hemodynamics (cardiac index, PAM, and stroke volume variation (SVV) and/or pulse pressure variation (PPV)], diuresis, and temperature. Other relevant data that include the types of anesthetic drugs used, type and volume of fluids, blood loss and transfusion requirements, need of vasoactive drugs, diuresis, nasogastric tube insertion, duration of surgery, mechanical ventilation time, number of recruitment maneuvers performed, and the need for rescue therapy will also be recorded.

### 8.6 General procedures

All participating patients, regardless of the study arm into which they are randomized, will be monitored and managed following general standard of care practices aimed at maintaining optimal conditions. Both intraoperative and immediate-postoperative (6h) anesthetic management (unrelated to ventilatory management) will be decided by the attending physician as they see fit, following the established protocols at each center. However, in order to ensure a high standard of anesthetic management, a number of common strategies have been established: halogenated agents will be given to maintain anesthesia, intra- and postoperative pain will be controlled with neuraxial anesthetics, fluids will be administered following goal-directed therapy principles. Appropriate antibiotic prophylaxis will be administered, and pharmacological prevention of postoperative nausea and vomiting (PONV) will be adopted. Finally, when nasogastric tube insertion is required, it should be withdrawn prior to extubation when possible. All these data will be collected and analyzed.

### 8.7 Monitoring

Intraoperative monitoring will include an electrocardiogram (ECG), pulse oximetry, capnography, bladder or esophageal temperature, anesthetic depth analysis (bispectral analysis, BIS) and a neuromuscular blockade (with train of four, TOF), invasive blood pressure measurements, and advanced hemodynamic monitoring with minimally invasive monitoring (optional depending on the standard clinical practice and availability of equipment at each hospital). Ventilatory parameters will be monitored by the anesthesia machine: VT, PEEP, $FiO_2$, peak airway pressure ($P_{aw}$), plateau pressure ($P_{plat}$), driving pressure (DP) and dynamic

compliance of the respiratory system ($C_{dyn}$). Postoperative monitoring will include at least an ECG, pulse oximetry, and invasive arterial pressure measurements.

**8.8 General intraoperative ventilator management**

Pre-oxygenation will be performed for 5 min at $FiO_2$ 1.0 with a tightly sealed face mask before induction. Patients will be ventilated in volume control mode (VCV) with squared flow, a VT of 8 ml/kg of the predicted body weight (PBW) during two lung ventilation and 5-6 ml/kg of the predicted body weight (PBW) during one-lung ventilation, PEEP of 4 $cmH_2O$ and a $P_{plat}$ of ≤25 $cmH_2O$. If the $P_{plat}$ reaches or exceeds 25 $cmH_2O$, VT will be decreased in 1 ml/kg steps until the $P_{plat}$ drops to ≤25 $cmH_2O$. The respiratory rate (RR) will be set to maintain an end-tidal carbon dioxide partial pressure ($EtCO_2$) between 35-45 mmHg, with an inspiratory to expiratory ratio (I:E) of 1:2 (it could be modified under the criteria of the attending physician) and a inspiratory pause time of 5-10% of the inspiratory time. $FiO_2$ will be set at 0.8 throughout the whole procedure. During the awakening period from general anesthesia (patients with spontaneous ventilation), a $FiO_2$ of 1.0 will be applied at the same end-expiratory pressure used, using either PEEP or CPAP. At the end of OLV a RM will be performed to ALL patients without a PEEP titration. The level of PEEP will be the same applied before the RM.

**In all the study patients adequate selective ventilation must be corroborated with the fiberoptic bronchoscope.**

Extubation will not be allowed by applying a positive pressure above the previously set PEEP or CPAP or while suctioning through the tracheal device. If necessary, aspiration can be performed at least 10 min before extubation. After suction, the patient will be switched back to mechanical ventilation. If the patient is randomized into the iOLA-iHFNC group, a new alveolar recruitment maneuver will be performed.

**Once extubation has been performed, all the study patients will be oxygenated with 0.5 $FiO_2$ through a Venturi mask during the first 30 minutes.**

**8.9 Specific intraoperative ventilatory management**

**STD-O2 group**

The patients will be ventilated as previously described in the general intraoperative ventilator management section.

**iOLA-iHFNC**

In this group, a RM is performed immediately after selective ventilation is initiated followed by a PEEP titration trial. Before the recruitment is performed the anesthesiologist must ensure that there is hemodynamic stability [mean arterial pressure (MAP) of more than 70 mmHg and/or a cardiac index of more than 2.5 ml/min/$m^2$] for at least 5 min, a stroke volume variation (SVV) of

less than 10%, and an adequate neuromuscular blockade (0 of 4 by TOF). The ARM is performed as described in the following section.

**8. 10 Alveolar recruitment maneuver (ARM)**

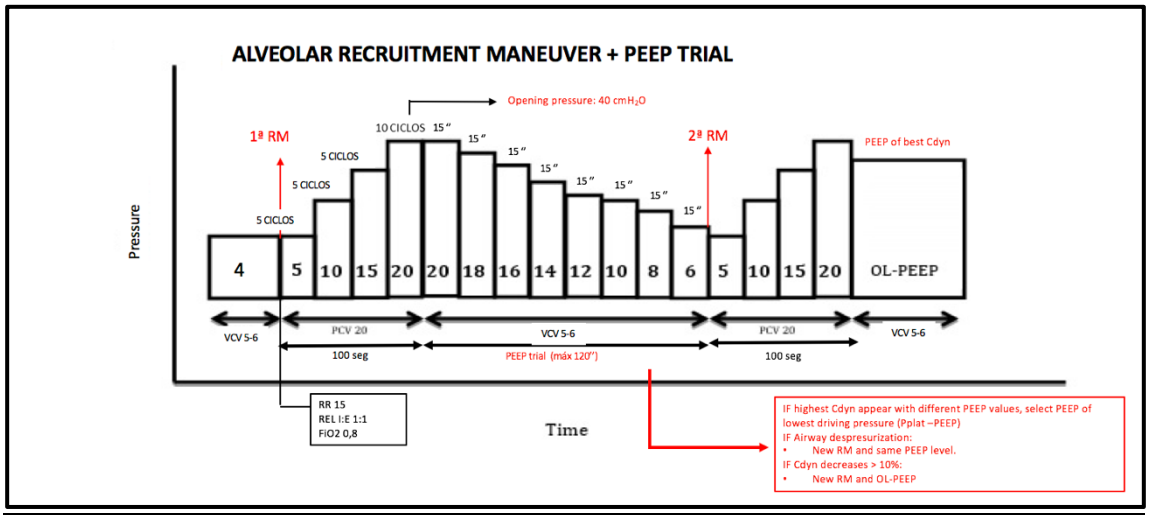
The ventilator will be changed from VCV to pressure-controlled ventilation (PCV) with a 20-$cmH_2O$ driving pressure and an RR of 15 breaths per minute (rpm), I:E of 1:1, 0.8 $FiO_2$, and PEEP of 5 $cmH_2O$. For the recruitment phase, the PEEP level will be increased in steps of 5 $cmH_2O$ every five respiratory cycles, up to a PEEP of 20 $cmH_2O$, to produce an airway opening pressure of 40 $cmH_2O$ and maintained for 10 respiratory cycles in the opening pressure (total maneuver time: 100 s). If hemodynamic instability appears during the recruitment phase (a >50% decrease in the cardiac index or MAP), the maneuver will be interrupted and 5-15 mg ephedrine or 0.05-0.15 mg phenylephrine given; after hemodynamic stabilization, a new ARM will be performed. After lung recruitment is accomplished, the optimal PEEP is titrated through a decremental PEEP trial, as described in the following section. (Figure 2).

**8.11 Titration of the optimal individual positive end-expiratory pressure: Decremental PEEP trial**

At the end of the last step of the PCV recruitment phase when the PEEP is 20 $cmH_2O$, the mode will be switched to VCV with a VT of 8 ml/kg, RR of 15 rpm, and I:E of 1:2, 0.8 $FiO_2$. After this, PEEP is decreased 2 $cmH_2O$ steps every 15 s until the highest $C_{dyn}$ observed on the ventilator's monitor (until $C_{dyn}$ starts decreasing or does not increase). ***In case that highest $C_{dyn}$ appears with several PEEP values, the PEEP with lowest driving pressure (Pplat – PEEP) will be seleted.*** Once the best $C_{dyn}$ is known, a new recruitment maneuver is performed and the PEEP for the best $C_{rs}$ is adjusted. In the case of accidental airway depressurization, a new ARM is performed while an identical PEEP is set (Figure 2).

The need of new recruitment maneuvers and a PEEP trial will be evaluated every 40 min by measuring the $C_{dyn}$. If there is a drop of more than 10% of the $C_{dyn}$, a new recruitment and PEEP trial will be performed.

Figure 2. Recruitment maneuver plus PEEP trial.




### 8.12 Intraoperative rescue maneuvers

In the case of arterial hypoxemia ($SpO_2$ of ≤92% with $FiO_2$ 0.8), after excluding endobronchial tube displacement, bronchospasm, pneumothorax, or a hemodynamic cause, a protocol for rescue therapy has been devised for each specific group.

**STD-O2 group**

The 0.1 $FiO_2$ is increased until $SpO_2$ is more than 95%. If arterial hypoxemia persists with 1.0 $FiO_2$, the PEEP is increased in steps of 2 $cmH_2O$ (until a maximum of 10 $cmH_2O$). If hypoxemia persists, a CPAP in the non-dependent lung is allowed.

**iOLA-iHFNC**

A new recruitment maneuver and PEEP trial will be performed. If $SpO_2$ is less than 92% (0.6 FIO2), $FiO_2$ is increased in 0.1 steps. If hypoxemia persists, a CPAP in the non-dependent lung is allowed.

**Lung Recruitment maneuver in the non-dependent lung**

If it is necessary to perform a lung recruitment maneuver for a leak test or as a rescue maneuver for hypoxemia, this will be done by connecting a CPAP system with adequate oxygen flow, increasing the level of CPAP in 5 cmH2O steps from 5 to 10 $cmH_2O$ every 5 seconds.
For leak tests, the lung will be thereafter depressurized again. If the maneuver is performed as a rescue maneuver the minimum level of CPAP that maintains an $SpO_2$ ≥92% will be adjusted.

### 8.13 General postoperative management in the postoperative care unit

General postoperative management in the postoperative care unit (PACU) or intensive care unit (ICU) not related to ventilator management will be decided by the attending physician following the established protocols at each center. Patients will be oxygenated with $FiO_2$ 0.5 through a

Venturi mask from extubation and during the first 15 to 30 min. The arterial oxygenation will be evaluated 15 to 30 min later when patients are awake and collaborative [Glasgow coma score (GCS) higher than 13] without any residual anesthetic effect (Richmond scale -1 to +1) and under pain control [verbal analog pain scale (*echelle visuelle analogique*; EVA) score <4] by decreasing the $FiO_2$ to 0.21 for at least 5 min (Air-Test). The Air-Test will not be performed if the patient already has an $SpO_2$ below 96% with $FiO_2$ 0.5. When the patient arrives in the PACU or ICU with invasive mechanical ventilation, the above-mentioned management will be applied after extubation.

**8.14 Specific postoperative ventilatory management**

**STD-O2 group**

Patients will be oxygenated through a Ventury mask with the minimum FIO2 that maintains a SpO2 ≥*92%*.

**iOLA-iHFNC group**

Supplemental oxygen at $FiO_2$ 0.5 will be delivered through a Venturi mask. During the first 6 postoperative hours [in the case of negative Air-Test ($SpO_2$ ≥97%)] the patient will be oxygenated with the minimum $FIO_2$ to maintain an $SpO_2$ ≥92%. In the case of positive Air-Test ($SpO_2$ ≤96%), high-flow oxygen therapy (HFNC) will be indicated with a flow rate of ≥ 50 lpm and with the minimum $FIO_2$ to maintain a $SpO_2$ ≥92%.

**Postoperative rescue maneuver**

In patients with persistent hypoxemia and/or hypercapnia [blood partial pressure of carbon dioxide ($PaCO_2$) >50 mmHg with a pH <7.30], tachypnea (RR >25 rpm), or increased activity of accessory respiratory muscles are present, inspiratory support with noninvasive ventilation (NIV) will be started.

**Noninvasive ventilation (NIV)**

The ventilator (specific for NIV or with software for NIV) and interface for NIV will be chosen by the attending physician and based on hospital availability. Positive pressure will start with an inspiratory positive airway pressure (IPAP) of 5 $cmH_2O$ higher than the EPAP and will be increased in steps of 5 $cmH_2O$ up to 15 $cmH_2O$. The EPAP will be increased to a maximum of 10 $cmH_2O$ (15 $cmH_2O$ if the BMI exceeds 30).

**Invasive ventilation**

Direct tracheal intubation (without NIV trial) will be indicated if the patients also meet at least one of the following criteria:

1. Hemodynamic instability [a systolic blood pressure (SBP) <80 mmHg or <40% of the basal or vasoactive drug requirements for more than 2 h is required to maintain the SBP above 80 mmHg].
2. Ventricular arrhythmias with hemodynamic instability or ECG signs of myocardial ischemia.
3. GCS of less than 9.
4. Sedation requirement due to agitation.

Tracheal intubation after 1 h of NIV will be indicated in patients meeting at least one of the following criteria:

1. Severe hypoxemia ($SpO_2$ <92%).
2. Respiratory acidosis (pH <7.30 with a $PaCO_2$ > 50 mmHg)
3. Signs of distress with increased use of accessory respiratory muscles or paradoxical thoracic-abdominal respiratory movements.

**8.15 Sample Size**

Assuming a confidence level of 95%, a percentage of pulmonary complications of 18% at 7 days post-intervention, a total of 655 patients per group (intervention group and control group) are required to detect as significant, with a power of 80%, an absolute reduction of 5% in the prevalence of pulmonary complications. Assuming 5% of possible losses, the final sample size is 1380 patients (690 per group).

**8.16 Statistical analysis**

The characteristics of the patients will be described by frequencies and percentages, in the case of categorical variables, and using mean and standard deviation or median and interquartile range in the continuous variables, depending on normality. The categorical variables will be compared using Chi-square test or Fisher's test, and the magnitude of the association with relative risks or odds ratios will be established. Continuous variables will be compared using the Student's t test or the Mann-Whitney U test, depending on normality. The baseline characteristics of the control group and the intervention group will be compared, and in the case of finding any difference in potentially confounding variables, they will be included as adjustment variables in the corresponding multivariate models. The main outcome variable will be expressed as a proportion of complications together with a 95% confidence interval. A difference of proportions test will be done to compare intervention group and control group. Time-to-event variables such as time to primary or secondary outcome will be analyzed using Kaplan-Meier curves and Cox

proportional hazards models. Variables with different measures over time will be analyzed using mixed linear models. All analyzes will be done by intention to treat and the missing data will be imputed using multiple imputation methods when more than 5% appear in the primary or secondary outcome variables. A level of significance of $\alpha = 0.05$ will be considered.

**8.17 Monitoring Plan**

The monitoring plan is based on the modification of the limits of Haybittle-Peto for the paralysis of trials after the intermediate analysis in the second half of the inclusion period. The analysis of the main outcome variable will be presented to the Data and Safety Management Board (DSMB) blindly to the study groups. The intermediate analysis will be carried out once the efficacy variables of the first 655 patients have been obtained. If the intermediate analysis is significant ($P < 0.001$) both positively and negatively for the intervention group, the safety committee will be able to paralyze the inclusion of new patients.