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# BMJ Open Protocol for venoarterial ExtraCorporeal Membrane Oxygenation to reduce morbidity and mortality following bilateral lung TransPlantation: the ECMOToP randomised controlled trial

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## ABSTRACT

**Introduction** Lung transplantation (LTx) aims at improving survival and quality of life for patients with end-stage lung diseases. Venous arterial extracorporeal membrane oxygenation (VA-ECMO) is used as intraoperative support for LTx, despite no precise guidelines for its initiation. We aim to evaluate two strategies of VA-ECMO initiation in the perioperative period in patients with obstructive or restrictive lung disease requiring bilateral LTx. In the control 'on-demand' arm, high haemodynamic and respiratory needs will dictate VA-ECMO initiation; in the experimental 'systematic' arm, VA-ECMO will be pre-emptively initiated. We hypothesise a 'systematic' strategy will increase the number of ventilatory-free days at day 28.

**Methods and analysis** We designed a multicentre randomised controlled trial in parallel groups. Adult patients with obstructive or restrictive lung disease requiring bilateral LTx, without a formal indication for pre-emptive VA-ECMO before LTx, will be included. Patients with preoperative pulmonary hypertension with haemodynamic collapse, ECMO as a bridge to transplantation, severe hypoxaemia or hypercarbia will be secondarily excluded. In the systematic group, VA-ECMO will be systematically implanted before the first pulmonary artery cross-clamp. In the on-demand group, VA-ECMO will be implanted intraoperatively if haemodynamic or respiratory indices meet preplanned criteria. Non-inclusion, secondary exclusion and VA-ECMO initiation criteria were validated by a Delphi process among investigators. Postoperative weaning of ECMO and mechanical ventilation will be managed according to best practice guidelines. The number of ventilator-free days at 28 days (primary endpoint) will be compared between the two groups in the intention-to-treat population. Secondary endpoints encompass organ failure occurrence, day 28, day 90 and year 1 vital status, and adverse events.

**Ethics and dissemination** The sponsor is the Assistance Publique–Hôpitaux de Paris. The ECMOToP protocol version 2.1 was approved by Comité de Protection des Personnes

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The question is relevant, and equipoise exists between both strategies.
- ⇒ Blinding of patients and physicians is not feasible.
- ⇒ The primary endpoint is objective and clinically relevant.
- ⇒ Non-inclusion criteria, secondary exclusion criteria and venoarterial extracorporeal membrane oxygenation initiation criteria in the control 'on-demand' group were determined after a Delphi survey among investigators.
- ⇒ We aim to evaluate this strategy under real-life clinical practice conditions but with a thorough methodology.

Ile de France VIII. Results will be published in international peer-reviewed medical journals.

**Trial registration number** NCT05664204.

## INTRODUCTION

### Background

Lung transplantation (LTx) is the only therapeutic option that can restore lung function and improve survival of patients with end-stage lung disease. Nevertheless, LTx remains a highly hazardous procedure. Significant complications might occur intraoperatively or during the postoperative period. The surgical procedure of LTx is challenging. Intraoperatively, the single-lung ventilation of a damaged lung followed by the reperfusion of the allograft can be associated with ventilatory difficulties, haemodynamic instability, ischaemia-reperfusion injury and early primary graft dysfunction (PGD).<sup>1</sup> Significant haemodynamic instability periods might also



occur because of pulmonary artery clamping, mechanical pressures on the heart, systemic consequences of lung reperfusion after ischaemia, blood loss associated with pneumonectomies, reperfusion of the graft and bleeding associated with pleural adhesions.

Double LTx was historically performed en bloc under cardiopulmonary bypass (CPB). The modern technique of sequential double LTx (SDLTx) can be performed off-pump or with a mechanical circulatory support. Intraoperative mechanical circulatory support allows for limiting haemodynamic instabilities, improving oxygenation and decarboxylation, and controlling the critical phase of reperfusion.<sup>1–3</sup> CPB has now widely been replaced by venoarterial extracorporeal membrane oxygenation (VA-ECMO), a simpler technique, requiring low levels of intraoperative anticoagulation associated with low levels of inflammation and leading to low rates of PGD, bleeding, renal failure, tracheostomy, intubation time and hospital stay.<sup>3</sup>

LTx for primary pulmonary hypertension is systematically performed under CPB or ECMO. For the other indications of LTx, some procedures might be performed entirely off-pump, whereas some are planned to be performed off-pump but require an intraoperative conversion to VA-ECMO support.<sup>4</sup> Unplanned intraoperative conversion to VA-ECMO support has been found to impair prognosis.<sup>4,5</sup> Because no precise guidelines for initiating intraoperative ECMO during LTx exist, the rate of LTx performed off-pump varies widely among centres, ranging from exceptional up to more than 70%<sup>2,4–9</sup> depending on experts' opinion and centre policy.

According to recent publications, the systematic use of intraoperative VA-ECMO may be associated with a low rate of PGD.<sup>10</sup> This hypothesis builds on two clinically observed mechanisms: (1) VA-ECMO implanted before pneumonectomy of the transplanted side allows for maintaining physiological perfusion of end organs, avoiding right heart failure and haemodynamic instability as well as hypoventilation until reperfusion of the first implanted lung; and (2) maintaining VA-ECMO during pneumonectomy and the implantation of the second side avoid the development of pulmonary oedema of the first implanted lung by reducing overflow and pressure-related injuries. However, VA-ECMO increases systemic inflammation and the risk of bleeding and transfusion due to systemic anticoagulation and large-vessel cannulation.

We aim at evaluating two strategies of VA-ECMO initiation in the intraoperative period in patients with interstitial lung disease (ILD) or chronic obstructive pulmonary disease (COPD)/emphysema requiring SDLTx: a control 'on-demand' strategy, in which VA-ECMO will be initiated on high haemodynamic or respiratory needs thresholds, and an experimental 'systematic' strategy in which VA-ECMO will be pre-emptively initiated at the beginning of the surgery.

## Hypothesis for the study

We hypothesise that systematic early intraoperative VA-ECMO implantation for patients with COPD/emphysema or ILD undergoing SDLTx would reduce the need for invasive mechanical ventilation in the first 28 days after surgery without increasing adverse events as compared with on-demand intraoperative VA-ECMO implantation.

## Study objectives

The primary objective is to assess the efficacy of a systematic early intraoperative VA-ECMO implantation strategy on increasing ventilator-free days in the 28 days after SDLTx as compared with an on-demand intraoperative VA-ECMO strategy guided by haemodynamic and respiratory parameters.

The secondary objectives are to study the impact of a systematic VA-ECMO strategy compared with an on-demand implantation strategy on the following:

- The occurrence of PGD grade 3 within 72 hours after LTx.
- All-cause mortality on day 28, day 90 and 1 year after LTx.
- The occurrence of ECMO-associated adverse events up to day 28, defined as cannula infection, cannula misplacement, air embolism, limb ischaemia, vascular complications and thrombophlebitis.
- The occurrence of ventilator-associated pneumonia up to day 28.
- The occurrence of intraoperative haemodynamic failure.
- The occurrence of postoperative haemodynamic failure up to day 28.
- The occurrence of acute renal failure (Kidney Disease: Improving Global Outcomes (KDIGO) stage 3<sup>11</sup>) up to day 28.
- The need for red blood cell transfusion up to day 28.
- ECMO-free days up to day 28.
- The length of intensive care unit (ICU) stay.
- The length of hospital stay.
- The occurrence of a bronchial complication requiring bronchoscopic intervention from LTx to 1 year.
- Forced expiratory volume in 1 s (FEV<sub>1</sub>) at 1 year.

## METHODS

### Study design

ExtraCorporeal Membrane Oxygenation to reduce morbidity and mortality following bilateral lung Transplantation (ECMOToP) is a prospective multicentre randomised, open-label, controlled superiority clinical trial comparing two strategies for patients with COPD/emphysema and those with ILD undergoing SDLTx on the basis of two parallel groups:

- Experimental group, systematic ECMO: VA-ECMO will be implanted systematically before the clamping of the first pulmonary artery.
- Control group (on-demand ECMO): VA-ECMO will be implanted intraoperatively, in an unplanned

manner if haemodynamic or respiratory indices meet preplanned criteria at different time points.

We report the study protocol according to the Standard Protocol Items: Recommendations for interventional Trials (SPIRIT) statement.<sup>12</sup>

## Definitions

'ECMO-related adverse events' are defined as cannula infection, misplacement, intraoperative or per ECMO-confirmed or suspected air embolism,<sup>13</sup> limb ischaemia, vascular complications or thrombophlebitis.<sup>4 5 7 9 14</sup>

'PGD' is defined according to International Society for Heart and Lung Transplantation<sup>1</sup> (online supplemental table 1). A 'bronchial complication' is defined by the occurrence of bronchial dehiscence; bronchial stenosis requiring interventional bronchoscopy under general anaesthesia to perform balloon dilatation, local laser therapy, electrocauterisation, argon plasma coagulation, cryotherapy, or mechanical debridement or placing an endobronchial stent; or bronchomalacia requiring invasive therapy (airway stenting or tracheobronchoplasty).<sup>15 16</sup> 'Ventilator-associated pneumonia' is defined as microbiologically confirmed pneumonia occurring under invasive ventilation<sup>17</sup> and after 48 hours of invasive ventilation.

## Participating units

This study will be implemented in seven of the nine French LTx programmes. These centres are used to collaborate on the topic on LTx, including for research led by the investigators of this project.<sup>18 19</sup> All centres belong to the Transplantation Group of the Société de Pneumologie de Langue Française and the Transplantation Group of the Société Française de Chirurgie Thoracique et Cardio-Vasculaire. All the investigators from the seven centres (surgeons, anaesthesiologists, intensivists and pulmonologists) agreed to participate and agreed on the whole design of the study. The investigators have been surveyed to acknowledge the criteria to initiate VA-ECMO in the on-demand group.

## A Delphi consensus for inclusion and exclusion criteria, secondary exclusion criteria and VA-ECMO initiation in the on-demand group

To precisely define non-inclusion criteria, secondary inclusion criteria and VA-ECMO initiation criteria in the on-demand group that were acceptable to the investigators, a Delphi consensus was used. Three panels were surveyed: a panel of anaesthesiologists and intensivists, one of pulmonologists and one of surgeons from the participating centres. The precise methods and results of the Delphi survey are detailed in the online supplemental methods and table 2.

## Study population

Eligible patients are adults ( $\geq 18$  years of age) with COPD/emphysema or ILD being assessed for SDLTx.

## Inclusion and exclusion criteria

Inclusion criteria:

1. Age  $>18$  years.
2. Assessed for SDLTx for COPD/emphysema or ILD.
3. Affiliated to the French social security.
4. Written informed consent.

Exclusion criteria:

1. At listing:
  - Pulmonary hypertension with mean pulmonary artery pressure (mPAP)  $>45$  mm Hg, including in the absence of haemodynamic collapse (normal mean arterial pressure (MAP), left ventricular ejection fraction, right ventricular (RV) function).
  - Pulmonary hypertension with echocardiographic evidence of right heart dysfunction (paradoxical septum or RV dilatation or RV ejection fraction (RVEF)  $<35\%$ ).
  - Pre-capillary pulmonary hypertension at right heart catheterisation with low cardiac output.
2. Redo LTx
3. Combined multiorgan transplantation
4. Active malignancy
5. Pregnancy, breast feeding
6. Patients under guardianship

Before inclusion, the inclusion and exclusion criteria will be checked, and investigators will access a centralised, secure, interactive, web-response system accessible from each study centre (CleanWEB, Telemedicine technologies, Boulogne-Billancourt, France)<sup>20</sup> and fill out a short electronic case report form.

## Recruitment

The screening visit will take place during the pulmonologists' or surgeons' visit before registration on the LTx waitlist, between 3 months and the day of inclusion visit. All patients would have undergone an in-depth clinical and paraclinical evaluation according to each site's practice. The cardiac evaluation before listing will encompass, as usual, at least an echocardiography evaluation and coronary angiography or coronary CT angiography. This consultation might take place several months before listing. If the anticipated time to listing is  $\leq 3$  months, the eligibility criteria will be checked, and if all inclusion and exclusion criteria are met, the patient will be asked to participate. If the patient agrees, informed consent will be collected the same day. A pregnancy test will be performed at the screening visit in women of childbearing age who do not receive any contraception.

If the patient is deemed not listable at this preoperative consultation, a new consultation with the surgeon will occur at listing. Eligibility criteria will be checked, informed consent will be collected and the patient will be included if possible.

## Randomisation

Randomisation will be performed in the operating room for LTx. We will randomise patients without pulmonary hypertension or with pulmonary hypertension



but without RV dilatation on echocardiography in the previous 6 months. The other patients will be randomised after the assessment of secondary exclusion criteria by the surgeon and the anaesthesiologist, before beginning the LTx. The secondary exclusion criteria will be checked after anaesthesia induction and before incision, in bipulmonary ventilation, in a patient with optimised volaemia status, haemoglobin level and ventilation management.

Secondary exclusion criteria are as follows:

1. Preoperative severe pulmonary hypertension with haemodynamic collapse on echocardiography defined by paradoxical septum or dilatation of the right ventricle or RVEF <20%.
2. ECMO as bridge to transplantation.
3. Hypoxaemia with arterial oxygen pressure ( $\text{PaO}_2$ ) / fractional inspired oxygen ( $\text{FiO}_2$ ) <80 mm Hg after induction.
4. Hypercarbia with arterial  $\text{CO}_2$  pressure >80 mm Hg after induction.

If no secondary exclusion criteria are present, each patient will be randomly assigned in a 1:1 ratio to the experimental (systematic) group or the control (on-demand) group. Randomisation and concealment will be achieved by using a computer-generated web-response system.<sup>20</sup> The randomisation will be balanced in various-sized blocks, with block size kept confidential, and stratified on centre and the underlying disease (restrictive or obstructive). At randomisation, investigators will access the website using an individual password and fill out the electronic case report form. The randomisation day is study day 0.

### Blinding

The study will be open label. Blinding of the investigator is not feasible and blinding of the patient is difficult to set up because in case of femoral cannulation, the patient will have a scar at the cannulation sites (groin area). However, the open-label design is not expected to modify the physician prescription and weaning of mechanical ventilation because among the goals of ICU physicians, the weaning of invasive ventilation is of paramount importance. Statistical analyses will be conducted with blinding to treatment assignment, with treatment groups denoted by letters instead of explicit labelling. All investigators will be unaware of aggregate outcomes during the study.

### Study interventions

The study overview is summarised in figure 1.

#### LTx procedure

The LTx procedure will be conducted according to the state-of-the-art<sup>21</sup> and each centre's practice, in a similar manner, whatever the randomisation group. See for details of monitoring in online supplemental file 1.

#### VA-ECMO initiation

In the experimental arm, VA-ECMO will be implanted electively, before pulmonary artery cross-clamp, systematically. In the control arm, VA-ECMO will be implanted

intraoperatively, in an unplanned manner if the haemodynamic and respiratory indices meet preplanned criteria at different time points. These criteria were validated by a Delphi panel survey (details below and in online supplemental file):

1. mPAP >50 mm Hg or two-thirds of MAP at monitoring, after induction and before incision in double-lung ventilation, 5 min after the first pulmonary artery is clamped and 5 min after the second pulmonary artery is clamped.
2. Right-left ventricle interdependence (RV dilatation with decrease in cardiac output) at transoesophageal echocardiography after induction and before incision in double-lung ventilation, 5 min after the first pulmonary artery is clamped and 5 min after the second pulmonary artery is clamped.
3.  $\text{PaO}_2/\text{FiO}_2$  ratio <100 mm Hg, at 5 min after the first pulmonary artery is clamped and 5 min after the second pulmonary artery is clamped.
4. Acute cardiogenic failure.

These criteria will be checked in a patient with optimised volaemia status, haemoglobin level and ventilation management (including with inhaled nitric oxide (NO)), at three prespecified times for criteria 1, 2 and 4: (1) after induction and before incision in double-lung ventilation, (2) 5 min after the first pulmonary artery is clamped and (3) 5 min after the second pulmonary artery is clamped. Criteria 3 will be checked at times (2) and (3). These criteria can also be checked whenever necessary during surgery, provided the pulmonary arteries are not clamped and the ventilation is not selective. Whenever these criteria are reached, the physician in charge should be sure that the volaemia status, haemoglobin level and ventilation management are optimised,<sup>4</sup> including with inhaled NO, according to usual haemodynamic and respiratory monitoring.<sup>22</sup>

#### VA-ECMO initiation, management and weaning, in both randomisation groups

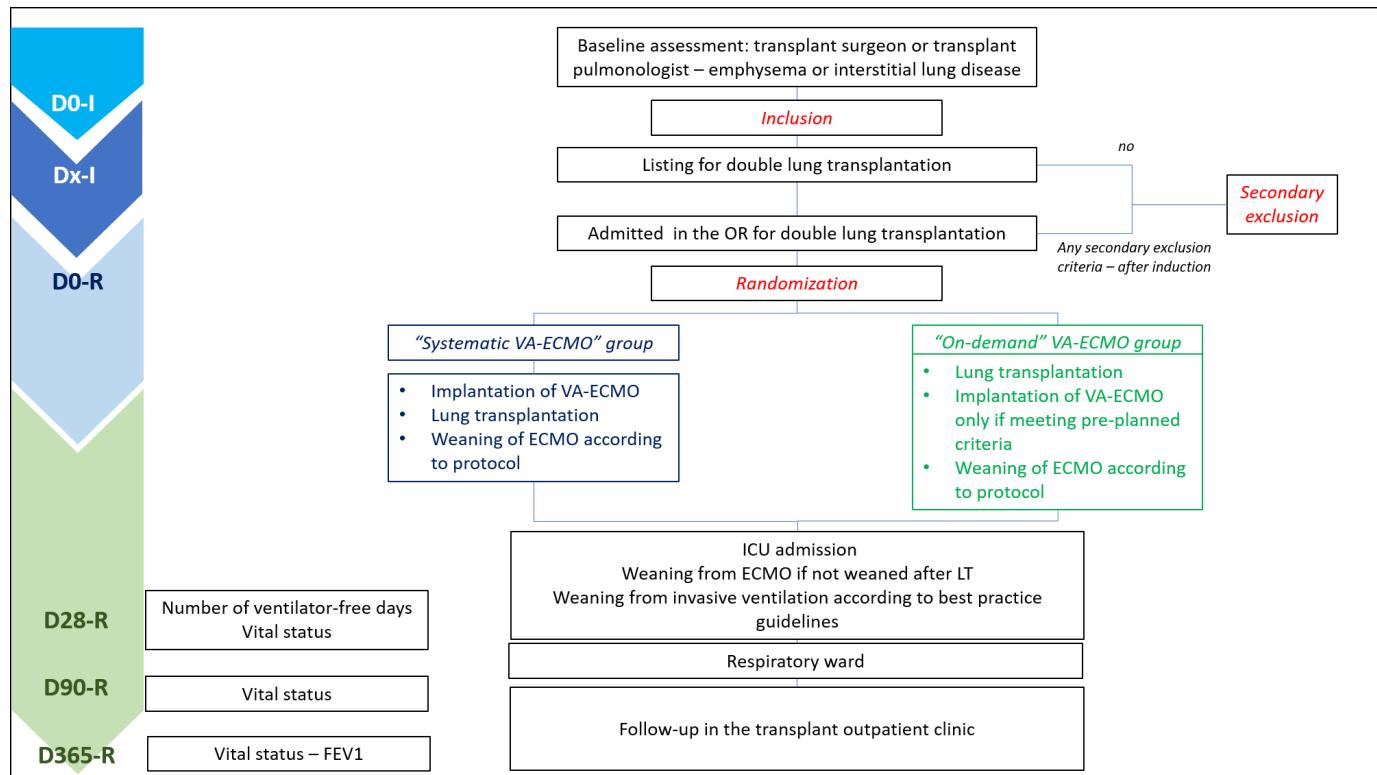
The procedure for the initiation and management of VA-ECMO is detailed in the online supplemental file 1 for patients requiring VA-ECMO.

#### Weaning from mechanical ventilation

If the patient is under VA-ECMO or veno-venous (VV)-ECMO at the end of the LTx procedure or still under mechanical ventilation, the patient will be transferred to the ICU under invasive mechanical ventilation. The patient will be weaned from mechanical ventilation according to best practices and French guidelines,<sup>23</sup> whatever the randomisation group, after explantation of ECMO support.

#### Data collection and follow-up

Collected data at each time are summarised in the SPIRIT schedule of events in table 1 and detailed in the online supplemental file 1 table 1



**Figure 1** Study protocol and randomisation arms. The screening visit will take place during the surgeons' or pulmonologists' visit before registration on the bilateral lung transplantation (LT) wait list. If all inclusion criteria and exclusion criteria are met, the patient will be asked to participate. If the patient agrees, informed consent will be collected. At operating room (OR) admission for the LT, the secondary exclusion criteria will be checked before randomisation according to the echocardiographic evaluation and arterial blood gas findings, after anaesthetic induction and before the beginning of surgery. If no secondary exclusion criteria is met, the investigator in charge (surgeon or anaesthesiologist) will randomise the patient to one of the treatment groups before beginning the LT procedure. For patients randomised to the experimental group ('systematic' ECMO), VA-ECMO will be implanted systematically before pulmonary artery cross-clamp; for patients randomised to the control group ('on-demand' ECMO), VA-ECMO will be implanted intraoperatively, in an unplanned manner if the haemodynamic and respiratory indices meet preplanned criteria at different time points. ECMO, extracorporeal membrane oxygenation; FEV<sub>1</sub>, forced expiratory volume in 1 s; ICU, intensive care unit; VA, venoarterial; VV, veno-venous.

#### At inclusion

Demographic data, the main medical history and the eventual extrarespiratory conditions will be recorded, as will be haemodynamic and respiratory parameters at listing.

#### At randomisation

In the operating room for LTx, secondary exclusion criteria will be checked before randomisation according to the echocardiographic evaluation and arterial blood gas findings. The recipient, donor and harvested lung data collected after randomisation are detailed in the online supplemental file 1.

#### At the end of the surgical procedure

For patients of both randomisation groups, the characteristics of the surgery performed and treatment administered will be collected. For patients in the experimental group, information on the actual implantation of VA-ECMO will be collected, and the reason for non-implantation will be collected if necessary. For patients in the control group, information on meeting the predefined criteria to initiate

ECMO and the actual implantation of VA-ECMO will be collected. In all patients who underwent intraoperative VA-ECMO, the characteristics of the VA-EMCO will be recorded.

#### At follow-up visits: daily until day 28

A daily clinical, radiological and biological evaluation of the patients will be performed as part of routine care, until day 28.

#### At month 3, ±1 week visit after randomisation

A visit will take place in the outpatient clinic as part of standard care.

#### At 1 year, ±30 days after randomisation

The last follow-up visit will be performed in the outpatient clinic as part of care.

#### Study endpoints

##### Primary endpoint

The primary endpoint is the number of ventilator-free days during the 28 days after LTx, defined as the number

**Table 1** Summary of data collected at each time point according to the SPIRIT schedule of events

Time point	Screening visit	Inclusion visit	On the day of LTx D0-R: allocation of randomisation arm	Immediately after surgery	Daily until D28-R	Month 3	Year 1
Information	X	X					
Informed consent		X					
Verification of inclusion and exclusion criteria		X					
Baseline variables: demographic data, medical history, haemodynamic assessment, respiratory assessment		X					
Verification of secondary exclusion criteria: clinical examination, haemodynamic assessment (right heart catheterisation, transoesophageal echocardiography) and respiratory assessment (arterial blood gas)			X				
Donor and harvested lung(s) characteristics (type and cause of death, age, height, last PaO <sub>2</sub> /FiO <sub>2</sub> ratio before organ harvesting, tobacco consumption, body mass index, Oto score <sup>27</sup> )			X				
Planned surgery, performance of an ex vivo lung perfusion procedure			X				
Type of surgery finally performed (single or double lung, surgical approach), length of ischaemia, length of surgery, intraoperative doses of vasopressors (epinephrine and norepinephrine), blood product extubation at the end of surgery				X			
Control group: VA-ECMO actually implanted, and if not, why?					X		
Experimental group: were the predefined criteria met to initiate ECMO? And if yes, was the VA-ECMO actually implanted?					X		
All patients who underwent intraoperative ECMO: were the weaning criteria met, and if so, was the ECMO explanted?					X		

Continued

**Table 1** Continued

Time point	Screening visit	Inclusion visit	On the day of LTx D0-R: allocation of randomisation arm	Immediately after surgery	Daily until D28-R	Month 3	Year 1
Outcome variables: ventilation status, need for postoperative VA-ECMO or VV-ECMO, presence and grade of primary graft dysfunction, occurrence of a surgical complication, need for surgery, need for red blood cells, need for other blood products, ongoing therapies, amount of vasopressor (epinephrine and norepinephrine) infused per day, need for renal replacement therapy, presence of a nosocomial infection, including a ventilator-associated pneumonia					X		
ECMO-related adverse event		X		X	X	X	X
Bronchial complication				X	X	X	
Vital status				X	X	X	
Forced expiratory volume in 1 s							X

ECMO, extracorporeal membrane oxygenation; FiO<sub>2</sub>, fractional inspired oxygen; LTx, lung transplantation; PaO<sub>2</sub>, arterial oxygen pressure; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; VA, venoarterial; VV, veno-venous.

of days alive and without invasive mechanical ventilation from LTx to day 28. We will assign 0 days free from invasive mechanical ventilation to patients who died during the follow-up period.

#### Secondary endpoints

1. The occurrence of PGD grade 3 during the first 72 hours after LTx. PGD grade 3 is defined according to clinical, biological and radiological criteria.<sup>1</sup>
2. Vital status at day 28 after LTx.
3. Vital status at day 90 after LTx.
4. Time to death from all causes within the first year after LTx.
5. ECMO-associated adverse events assessed daily from day 1 to day 28 and at day 90.
6. Occurrence of ventilator-associated pneumonia from LTx to day 28.
7. Intraoperative level of epinephrine or norepinephrine (dose in µg/kg body weight).
8. Catecholamine-free days (number of days without epinephrine or norepinephrine administration) from LTx to day 28.
9. KDIGO stage 3<sup>11</sup> renal failure-free days up to day 28.
10. Number of red blood cell packs administered from LTx to day 28.
11. VV-ECMO or VA-ECMO-free days from LTx to day 28.

12. Length of ICU stay in days (from LTx to ICU discharge).
13. Length of hospital stay in days (from LTx to hospital discharge).
14. Bronchial complications requiring bronchoscopic intervention from LTx to 1 year.
15. FEV<sub>1</sub> at 1 year.

#### Safety considerations

Safety considerations are detailed in online supplemental file 1. Among secondary endpoints, some are designed to investigate the safety of the experimental arm, as described.<sup>4 7–9 14</sup> Some will be specifically examined. A data safety monitoring board is established for this trial to oversee the trial's safety.

#### Sample size calculation

The mean number of ventilator-free days between day 1 and day 28 in patients who underwent LTx in Bichat Hospital in 2018 for an SDLTx is estimated at 20.9 days (SD 9.9) (unpublished data). To show an increase of 22% (ie, 4.6 days) (clinically relevant) of ventilator-free days in the experimental group, we need 198 patients (99 per group), assuming a common SD between the two groups (SD 9.9), a type I error rate of 5% and a power of 90% by Student's t-test (superiority trial). No lost to follow-up



is expected for the primary endpoint because no patient will be discharged from the hospital before day 28 after LTx.

### Data analysis plan

A flow chart will describe the number of eligible patients and the number of patients actually included in the study and assessed at each visit in each of the two arms. For each randomisation group and at each assessment date, categorical variables will be reported with number (percentage) and quantitative variables with mean (SD) or median (IQR) if skewed distribution. This description will be performed for all patients and for each group. The number of missing values will be reported.

### Analysis of the primary endpoint

In the primary analysis, the ventilator-free days alive during the 28 days after LTx for patients randomised in the control group (systematic strategy) will be compared with the ventilator-free days alive during the 28 days after LTx for patients randomised in the experimental group (on-demand strategy) by a test of superiority (Student's t-test) at the 5% threshold. In this analysis, the number of ventilator-free days will be defined as the number of days without invasive mechanical ventilation at day 28. For patients who died before day 28, 0 ventilator-free days will be assigned.

Linear regression of the number of ventilator-free days with adjustment on randomisation stratification variables will be performed as a sensitivity analysis. The primary endpoint analysis will be adjusted on the stratification factors (centre and the underlying pathology (restrictive or obstructive)) and on potential confounders using a multivariate analysis (linear regression model). Potential confounders will be examined by using a directed acyclic graph.

### Analysis of the secondary endpoints

All secondary analyses will be performed for the intention-to-treat population (all randomised patients) and the per-protocol population (patients with no major deviation of the protocol) at a bilateral 5% alpha risk. Unless otherwise specified, categorical variables will be compared by  $\chi^2$  test or Fisher's test as appropriate. Continuous variables will be compared by Student's t-test or Wilcoxon test as appropriate. The detailed analysis of the secondary endpoints is in the online supplemental file 1.

### Missing data

Missing data will be described for the overall population and by treatment group as well as the method of handling them according to their frequencies and nature (including multiple imputations). Sensitivity analysis will confirm the reliability of conclusions upon various hypotheses for missing values. The missing secondary endpoints will not be replaced.

### Software

The analyses will be performed with R V.3.0 or a later version (R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org/>) or SAS V.9.2 or a later version.

### Data collection and management

Data collection will be performed in electronic format (see details in the online supplemental file 1).

### Patient and public involvement

Patients and the public are not involved in this protocol.

## DISCUSSION

We designed the ECMOToP trial to assess the efficacy of a systematic early intraoperative VA-ECMO implantation strategy on post-LTx morbidity as compared with an on-demand intraoperative VA-ECMO strategy guided by haemodynamic and respiratory parameters in patients with COPD/emphysema or ILD undergoing SDLTx. The VA-ECMO implantation strategy for LTx remains dependent on surgeon, anaesthesiologist and centre practices. Nevertheless, some evidence favours a systematic pre-emptive strategy. This trial aims to answer the question of the efficacy of a strict protocol to guide the implementation of ECMO in LTx.

The conflicting evidence stems from comparing a systematic strategy with a strategy without any support or a strategy of ECMO initiation in an unplanned manner. Hoetzenegger *et al* published a retrospective single-centre cohort study of 582 bilateral LTx operations performed between 2010 and 2016.<sup>7</sup> Three groups were compared: patients undergoing LTx without ECMO support, those undergoing LTx with a pre-emptively initiated ECMO strategy and in whom ECMO was weaned after LTx, and those in whom ECMO was prolonged after the end of LTx. Of note, 98 patients with intraoperative ECMO were matched to 98 without ECMO to balance pretreatment characteristics using propensity score matching. This analysis failed to find any significant difference between the two strategies: in  $\text{PaO}_2/\text{FiO}_2$  ratio on ICU admission or after 24 hours or in 1-year, 3-year and 5-year survival rates (89%, 85% and 85% vs 85%, 79% and 77%, respectively;  $p=0.290$ ). In a subgroup analysis by underlying disease, in patients with emphysema or ILD, the survival differences remained non-significant ( $p=0.841$  and  $p=0.129$ ). Similarly, Fessler *et al*<sup>8</sup> compared the outcomes of 300 patients according to the ECMO strategy applied for SDLTx. In this single-centre retrospective analysis, 209 patients did not require ECMO, 77 underwent unplanned intraoperative ECMO and 14 had ECMO in a pre-emptive systematic manner. Patients with unplanned intraoperative ECMO had significantly poorer prognosis than those with no ECMO, with higher rates of PGD grade 3 at 48 and 72 hours, greater length of postoperative mechanical ventilation and lower survival. Intraoperative ECMO, whether unplanned or planned, was an independent

risk factor for 3-year mortality. Of note, the prognosis of patients with pre-emptive ECMO and those with no ECMO did not significantly differ. Unfortunately, in this series, many confounding biases might not have been accounted for. Lastly, Ius *et al*<sup>4</sup> reported the results of a 5-year retrospective single-centre study of 595 patients who underwent LTx: 425 did not require ECMO, 95 had ECMO as a standardised pre-emptive strategy and 75 had unplanned ECMO, initiated intraoperatively. Although overall mortality did not differ significantly between groups, in-hospital mortality was higher for patients who underwent ECMO, either planned or unplanned, as compared with no ECMO. Moreover, unplanned ECMO was an independent risk factor for in-hospital mortality (OR 24 (95% CI 3 to 172); p=0.002). The same group expanded its analysis to provide long-term outcomes.<sup>9</sup> In increasing the number of analysed patients to 1161 (311 had ECMO), the authors confirmed the more complicated course of patients undergoing ECMO, with a significantly higher in-hospital mortality as compared with patients without ECMO (10.9% vs 2.3%; p<0.001). Those surviving to hospital discharge did not differ in long-term complications or outcomes. Although of high interest, all these data are subject to caution. Obviously, the caveat of retrospective studies is to gather patients with different disease severities, including those with very unstable disease who might have received ECMO too late in the unplanned ECMO strategy and those with very stable disease who might have done very well without ECMO in the systematic strategy.

The way to investigate the efficacy and safety of a systematic strategy is to implement a randomised rigorous protocol of management, with guidelines to initiate ECMO in the experimental group. Among strengths, our study encompasses a Delphi consensus to validate this protocol among investigators. We chose to allow a wide range of VA-ECMO devices and cannulation sites. Indeed, the type of ECMO and the site of cannulation have not had any significant impact on intraoperative or postoperative courses but mostly rely on centre protocols and team practices. Furthermore, we aimed to perform a pragmatic study, so the protocol should allow to include as many patients as possible in the targeted population. Lastly, because the cannulation site might not differ in a single centre according to local protocols, the different cannulation sites should be evenly distributed according to randomisation groups stratified by centre.

With a systematic VA-ECMO strategy, we expect a lower PGD stage after LTx<sup>1</sup> and thus a reduced time of mechanical ventilation and higher number of ventilator-free days during the first 28 days after LTx. An earlier liberation from mechanical ventilation after LTx would lead to reduced risks associated with mechanical ventilation (ventilator-associated events, including infection).<sup>24</sup> The main expected risk would be increased VA-ECMO-associated risks, as reported.<sup>14</sup> In the LTx field, the reported adverse events encompass cannulation vascular complications such as thrombosis or ischaemia, groin

infections or bleeding, either pleural or cerebral.<sup>4 7 8</sup> These risks have been found more prevalent in patients who underwent intraoperative ECMO but more importantly in patients who required prolonged VA-ECMO.<sup>7</sup> In our study, we assume that patients randomised in the systematic group and who cannot be weaned from ECMO after the surgery will have had prolonged ECMO with an on-demand strategy anyway. This assumption will be covered by the results of the study by comparing the occurrence of ECMO-related complications in both groups.

Our study protocol has some limitations. Blinding of patients and physicians is not feasible. In case of femoral cannulation, the patient will have a scar at the cannulation sites (groin area). However, an open-label design is not expected to modify the assessment of the primary endpoint. In a similar manner, a PROBE (Prospective Randomized Open, Blinded End-point) methodology<sup>25</sup> cannot be used, because a blinded review of the weaning criteria will lack the clinical evaluation, which is the rule in ICU management. In some situations, all weaning criteria can be met, but clinical expertise might lead to postponing extubation. A blinded adjudication committee might fail to understand a clinical decision retrospectively. Moreover, we chose to evaluate this strategy in real-life clinical practice conditions. Likewise, although cluster randomisation might allow for limiting contamination bias, we believe that because the different centres might have different surgical and ECMO cannulation practices, it seems important that in each centre, patients would be treated with both strategies. Finally, the weaning of mechanical ventilation is of paramount importance for ICU physicians, and every physician taking care of LTx recipients aims at reducing the exposure to invasive ventilation. Moreover, the weaning from mechanical ventilation will be performed according to best practices and according to French guidelines, those usually adopted in the participating centres.<sup>23</sup>

In conclusion, we are confident this trial will bring evidence to improve care of a highly vulnerable population. The efficacy of applying a systematic strategy on reducing mechanical ventilation during the 28 days after LTx, without increasing mortality or morbidity, would support future guidelines on the systematic use of ECMO in the early intraoperative period of SDLTx.

## ETHICS AND DISSEMINATION

### Legal obligations and approval

Sponsorship has been agreed by the Assistance Publique-Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department). AP-HP obtained the approval of the French medicine regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé; IDRCB no: 2022-A00538-35, 3 May 2022) and the ethics committee Comité de Protection des Personnes Ile de France VIII (registration no. 2022-A00538-35; date of approval 11 August 2022, updated 4 October 2023 for



the ECMOTO<sup>P</sup> protocol version 2.1; 19 September 2023). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission (details in the online supplemental file).

### Publication plan

Results will be published in international peer-reviewed medical journals, under the responsibility of the study coordinating investigator, with the agreement of the principal investigators and the methodologist. The coauthors of the reports and publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. Rules on publication will follow international recommendations.<sup>26</sup>

### Data sharing statement

Data may be obtained from a third party and are not publicly available. The full protocol, participant-level deidentified dataset and statistical code of this study will be available on reasonable request from the corresponding author.

### Trial status

Not yet recruiting. Inclusions are planned to start in 2023 and are expected to be completed in 2025.

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**Contributors** JM, PE and PMor drafted the manuscript. JM, PE, PMon and PMor participated in the design of the ECMOTO<sup>P</sup> Study and contributed to revisions of the original manuscript. PE performed the statistical plan and sample size calculation. DB, AC, JF, JJ, PL, OM, PP, HR, ES, JT, FT, MV, YC and HM edited the manuscript, read and approved the final manuscript, and will be involved in the acquisition of data.

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