Protocol

Randomized Clinical Trial of Intraoperative ECMO versus Cardiopulmonary Bypass in Lung Transplantation

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DEFINITIONS, ACRONYMS, AND ABBREVIATIONS

CPB Cardiopulmonary bypass
ECMO Extracorporeal membrane oxygenation
PGD Primary Graft Dysfunction

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ABSTRACT

Title	**Randomized Clinical Trial of Intraoperative ECMO vs. Cardiopulmonary Bypass in Lung Transplantation**
Background	Cardiopulmonary bypass (CPB) is the current standard of care for intraoperative cardiorespiratory support during lung transplantation. However, the blood-air interface and the need for full systemic anticoagulation may lead to systemic inflammatory response and coagulopathy. Some reports have suggested that intraoperative support with extracorporeal membrane oxygenation (ECMO) in lieu of CPB may be a better alternative with decreased bleeding, blood requirements and rates of primary graft dysfunction (PGD).
Hypothesis	patients on ECMO will have • decreased transfusion requirements, • decreased intubation time, • lesser PGD grade at 72 hours • No increase in major adverse events • Pump duration may be longer.
Study Design	A prospective randomized trial comparing intraoperative support with ECMO and CPB. This will be a superiority trial for efficacy and non-inferiority for safety. The allocation ratio will be 1:1.
Number of Participants	40 in each arm
Study Objectives	Determine if ECMO compared to CPB during lung transplantation has a beneficial effect on

	short term outcomes after lung transplantation.
Interventions	When patient need intraoperative cardiopulmonary support, patient would be randomized to ECMO or CPB
Inclusion Criteria	All patients undergoing lung transplantation. Not all patients randomized will need intraoperative support
Exclusion Criteria	Patients undergoing concomitant cardiac operations with indication for obligate use of cardiopulmonary bypass Patient with specific anatomy that require full cardiac decompression such as severe pulmonary hypertension or large heart that are shifted severely into the left chest (relative) Patients with high likelihood of significant pleural bleeding that will require returning the blood back into the cardiotomy reservoir (relative) Patients bridged to transplant with ECMO Patients who the surgeon feels would be better served with CPB rather than ECMO These patients will be entered into a registry and followed.
1 ° Endpoint	1 Bleeding: total PRBC transfusion requirements at 72hours
2 ° Endpoint	Superiority 1. Ventilation time (days) 2. Intraoperative PRBC transfusion rates 3. Duration of support 4. Primary graft dysfunction (PGD) grade at 72 hours. 5. Transfusion requirement of FFP, platelets, cryoprecipitate at 72 hours. Non-inferiority: 6. Composite outcome of: 30-day or discharge date (if earlier than 30 days) mortality, bleeding requiring

	reoperation, new ECMO, new renal failure requiring dialysis
Baseline and Clinical Outcomes Data	From: EDIT database, EPIC Medical records review

BACKGROUND AND SIGNIFICANCE

The Problem

In lung transplantation where cardiopulmonary support is needed intraoperatively, the usage of CPB is historically and still currently the standard of care at most centers worldwide.

While cardiopulmonary bypass allows for versatility and the conditions necessary to complete many transplant operations, there are disadvantages, such as the need for full dose heparinization with the associated risk of bleeding, and the activation of inflammatory mediators which have to potential to lead to higher degrees of postoperative primary graft dysfunction (PGD). To counter some of these complications, ECMO in a veno-arterial (VA ECMO) configuration has been proposed and studied as an alternative method of cardiopulmonary support. Prior reports have suggested that intraoperative support with extracorporeal membrane oxygenation (ECMO) in lieu of CPB may be a better alternative with decreased bleeding, blood requirements and rates of primary graft dysfunction (PGD).

Currently, many centers would use one technique or the other and both are considered current standard of care and best practice. At Cleveland Clinic, we have used both methods. The method of support is currently not discussed with patients as both are considered acceptable.

HYPOTHESIS

Our hypothesis is that patients on ECMO will have a decreased transfusion requirements, decreased intubation time, lesser PGD grade at 72 hours without increase in adverse risk. Pump duration may be longer.

ENDPOINTS

Primary

1 Bleeding: total PRBC transfusion requirements at 72hours

Secondary

Superiority

1. Ventilation time (days)
2. Intraoperative PRBC transfusion rates
3. Duration of support
4. Primary graft dysfunction (PGD) grade at 72 hours.
5. Transfusion requirement of FFP, platelets, cryoprecipitate at 72 hours.

Non-inferiority:

1. Composite outcome of: 30-day or discharge date (if earlier than 30 days) mortality, bleeding requiring reoperation, new ECMO, new renal failure requiring dialysis

STUDY DESIGN

Randomized clinical trial with an allocation ratio of 1:1, comparing CBP versus ECMO for intraoperative cardiopulmonary support. Study will have a superiority design for efficacy and a non-inferiority design for safety.

Randomization:
All lung transplant patients will be consented preoperatively. Patients will be randomized at the beginning of the case and the configuration of the cardiopulmonary bypass machine will be set accordingly. Not all patients randomized will require intraoperative cardiopulmonary support.

Circuit design:
separate tubing that connects the venous return line directly to the pump head bypassing the venous reservoir. The venous reservoir is still connected and but clamped.

Incision and cannulation:
The type of incision will be at the discretion of the surgeon but can be sternotomy, thoracotomy or clamshell. If patient has a sternotomy and randomized to ECMO, venous cannula should be placed through a percutaneous femoral venous cannula to avoid the potential of air embolus.

Anticoagulation:
ACT target 200-250. Repeat every 30 min. Bolus 5000U, give supplemental doses as needed.

Conversion to full cardiopulmonary bypass:
Give full dose heparin; release the clamp on the venous reservoir after act is above 480.

Reasons to convert from ECMO to CPB intraoperatively:

- Significant bleeding to allow blood to return back to circuit
- Heart remain too distended to allow mobilization
- Air in the circuit
- The need to fibrillate or arrest the heart
- Hemodynamic instability from positioning

Other safety mechanisms:

- Consider system for rapid transfusion
- Double lumen intubation: the heart does not decompress and there's ejection requiring the need for ventilation.
- Use an urchin or heartnet for heart positioning if necessary
- Once the patient is decannulated, the blood from the circuit can be re-transfused back into the patient

Transfusion triggers:
Transfusion triggers will be hematocrit of .24 and at the discretion of the staff surgeon, anesthesiologist or intensivist. Coagulopathy will be corrected based on Cleveland clinic post cardiotomy bypass protocol (appendix 2) and at the discretion of surgeon, anesthesiologist or intensivist.

Patients will be extubated at the discretion of the staff surgeon and intensivist.

Patients who are consented but not included in the study and patients who are felt to be better candidates for cpb will be followed in a separate registry

NUMBER OF PARTICIPANTS

40 Patients in each arm

Power calculation (based on 2015 CCF outcomes)

- Safety
  - 30 day mortality: 6.2%

Bleeding requiring reoperation: 10.3%
New ECMO: 1.3%
New renal failure requiring dialysis: 10.3%
Composite outcome 18.6%.

Sample size calculation
Non-inferior margin: 5%
90%: 283, 80%:205, 70%: 155
Non-inferior margin: 10%
90%: 77, 80%:56, 70%: 42

Efficacy

PGD grade at 72 h:

0: 24.4%
1: 47.4%
2: 14.1%
3: 14.1%

RBC transfusion

CPB: 14.7(8.4) vs ECMO 9.3(6.9)
90%: 51, 80%:39, 70%: 30

Ventilation time

CPB: 16.5days (27.3) vs ECMO 8.25 (16.4)
90%: 83, 80%:62, 70%: 49

For literature outcomes, see appendix 1.

STUDY POPULATION

The study population will be all patients undergoing lung transplantation at our institution. These patients will be randomized using the block method and allocated to either the CPB or ECMO group. Not all patients randomized will require intraoperative support.

Inclusion Criteria
All consented patients undergoing lung transplantation.

Exclusion Criteria

Patients undergoing concomitant cardiac operations with indication for obligate use of cardiopulmonary bypass

Patient with specific anatomy that require full cardiac decompression such as severe pulmonary hypertension or large heart that are shifted severely into the left chest (relative)

Patients with high likelihood of significant pleural bleeding that will require returning the blood back into the cardiotomy reservoir (relative)

Patients bridged to transplant with ECMO

Cystic fibrosis/bronchiectasis/resistant infection patients where surgeon will need to remove both lungs prior to implantation

Patients who the surgeon feels would be better served with CPB rather than ECMO
These patients will be entered into a registry and followed.

CLINICAL CENTERS

Patient Confidentiality
All patient records will be kept confidential according to HIPAA guidelines. Study investigators and site Institutional Review Boards (IRBs) may review source documentation as necessary, but will then transmit this information to Clinical Investigations at Cleveland Clinic according to the patient's unique study number. Linkage of that study number to the actual patient will reside only at the individual institutions. Aggregate data from this study may be published as per publication policy documented in the trial agreements; no data with patient identifiers will be published.

Consent
Patients will be consented for surgery ahead of time at time of listing

DATA COLLECTION

Data will be collected from Epic Systems chart review and supplemental data collection. All necessary data are currently already collected. Study terminates at patient discharge. No additional testing or followup is needed beyond what is already done for this patient population.

DATA MANAGEMENT

The data will be stored in Red Cap Sheets strictly secured and managed by the lead and other co-investigators. No identifiable information will be shared with outside parties, ensuring that all data will remain safely stored on Cleveland Clinic Main Campus user hard drives and will only be shared amongst our study team.

ANALYTIC PLAN

Basic statistical analysis will be required to compare the outcomes in the groups. Patients who are excluded will be included in a separate registry.
Analysis will be based on intention to treat.
A statistical significant difference is defined as a two-sided P value less than 0.05.

REFERENCES

1. Machuca (2015) Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation.

2. Bermudez (2014) Outcomes of Intraoperative Venoarterial Extracorporeal Membrane Oxygenation Versus Cardiopulmonary Bypass During Lung Transplantation.

3.Ius (2012) Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass.

4. Hoechter (2015) The Munich Lung Transplant Group: Intraoperative Extracorporeal Circulation in Lung Transplantation.

Appendix 1

Outcomes from Literature on CPB vs. CPB

	CPB	**ECMO**
Surgical time (min)	444	425
Heparin intraop (IU/kg)	490.1	54.6
ECC time (min)	203.5	216
Crystalloid (mL)	2484	3466
Colloid (mL)	1500	1300
Cell saver (mL)	690	500
Intraop Transfusion (units)	PRC 9 units FFP 8.5 units Platelets 3.5 units FibGen 5 (g) PPSB 3 (IU) TXA 2.5 (mg)	PRC 6 FFP 9 Platelets 2 FibGen 0 (g) PPSB (prothrombin complex concentrate) 0 (IU) TXA 2 (mg)
Overall Transfusion (units)	PRC 16 FFP 13 Plts 4 FIbGen 4 PPSB 2.5 (IU) TXA 2.5 (mg)	PRC 8 FFP 15 Plts 2 FIbGen 0 PPSB 0 (IU) TXA 2 (mg)
ECMO prolonged into postop (n)	6	15
→Duration of prolonged ECMO (days)	4	3
→Graft failure/reperfusion injury (n) (indication for prolonged ECMO)	2	9
→pHT /hemodynamic (n) (indication for prolonged ECMO)	4	6
Redo-surgery (n)	15	13
Ventilator support (days)	21	4.5
ICU LOS (days)	36	14.5
ICU free survival (days)	54	72
Hospital LOS (days)	47	42.5
Hospital free survival (days)	14	36.5
30 day mortality (n)	1	3
One year mortality (n)	4	5

Hoechter (2015): ECMO perioperative advantages (CPB higher transfusion, ventilator support, ICU stay), long-term not affected (same 30 day and 1 year mortality); excluded bridge to ECMO; * 2 analyses (1) CPB and ECMO (2) full-dose and low-dose heparinization during ECC; (better outcomes in ECMO related to heparin use not the ECC device; yet independent of heparin the ECMO still better at reducing PGD/hemodynamic instability (retrospective, N=188)

	CPB	**ECMO**

Intraop ischemic time (min)	363	375
ECC support (min) mean	232.5	366.6
Intraop transfusion (units)	RBC 5.9 FFP 3.1 Platelets 8	RBC 7.7 FFP 3 Platelets 4
Periop transfusion (72 hrs) (units)	RBC 14.9 FFP 9.3 Platelets 11	RBC 13 FFP 8.4 Platelets 10.7
Postop initial ventilation (hrs)	226	184.7
Reintubation (n)	80 (36%)	10 (20%)
Postop total ventilation (hrs)	380	250
ICU LOS	21.9	15
Hospital LOS (days)	43	41
Reoperation for bleeding (n)	39 (17%)	4 (8.2%)
Postop renal failure requiring dialysis (n)	49 (22%)	4 (8%)
Postop ECMO (severe PGD) (n)	34 (15%)	9 (18%)
30 day mortality (n)	11 (5%)	2 (4%)
1 year mortality (n)	42 (19%)	9 (19%)

Bermudez (2014): ECMO decreased pulmonary (reintubation)/renal complications, (same severe PGD, perioperative rbc transfusion, mortality long term 30d 6m), longer time on support / more RBC intraop transfusion for ECMO(included cardiac procedures) (CPB n= 222, ECMO n=49)

	CPB	**ECMO**
Ischemic time (min)	518 L, 432 R, 495 single lung	581 L, 450 R, 400 single lung
ECC time	162 min	Not given
Intraop transfusion (units)	PRBS 12 2.5 platelet concentrate 7.2 FFP 2 fibrinogen	PRBS 7.1 1.5 platelet concentrate 7.1 FFP 1.6 fibrinogen

	4 prothrombin complex concentrate	3.7 prothrombin complex concentrate
Postop transfusion (units)	PRBC 17.9 PC 4.8 17.6 FFP Fibrinogen 0.6 (g) prothrombin complex concentrate 1.3	PRBC 12.7 PC 3.3 11.1 FFP Fibrinogen 0.5 (g) prothrombin complex concentrate 2.7
New postop ECMO support	26%	4%
Postop VA ECMO (n)	1 (2%)	19 (41%)
Rethoracotomy for bleeding (n)	16 (35%)	9 (19)
New requirement for dialysis (n)	22 (48%)	6 (13%)
Ventilation time (days)	21.4	14
ICU LOS (days)	29	19
In-hospital mortality	39%	13%
Survivors at discharge (n)	28 (61%)	40 (87%)
Survival rate at 3 months (%)	70%	87%
Survival rate at 12 months (%)	56%	81%

Ius (2012): 2 groups; significant in hospital mortality reduction with ECMO , lower rates of PGD and renal failure. ECMO better periprocedural management, less postop complications; increased survival despite greater preoperative morbidity, transfusion req, postop complications (hemodyalisys) (did not exclude cardiac procedure) (N=46 CPB and ECMO groups)

	CPB	**ECMO**
Intraop pump time (min)	199	210
Warm ischemic time (min)	69 L, 64 R, 74 single	73 L, 70 R, 74 single
Intraop Transfusion (units)	6 pRBC 1 Platelets 4 FFP	3 pRBC 0 Platelets 0 FFP
Postop Transfusion up to 72 hrs	2 pRBC	1 pRBC
Length of mechanical ventilation (days)	7.5	3
ICU LOS (days)	9.5	5
Hospital LOS (days)	27	19

Extracorporeal life support postop requirement (n)	5	0
Dialysis req (n)	12 (18%)	3 (9%)
Reoperation for bleeding (n)	18 (27%)	3 (9%)
90 day mortality (n)	10 (15%)	2 (6%)

Machuca (2015): ECMO may be considered as first choice cardiorespiratory support during LT a. Excluded: patients bridged w extracorporal life support, required emergency cannulation for cardiopulmonary support, concomitant cardiac procedure/transplant, B cenocepacia; b.Matched: age, lung transplantation indication, procedure type (bil/single), Recipient factors similar (BMI, gender, donor info) c. Outcomes i.Perioperative: blood product transfusion ii.Early outcomes: mechanical ventilation requirement, ICU stay, hospital stay iii. 90day mortality (33 ECMO matched with 66 CPB)

Appendix 2:

Post Cardiopulmonary Bypass Coagulopathy Protocol

CCF TEG Normal Values:

R time: 2-8 mins
K time: 1-3 mins
Angle: 55-78 degrees
MA: 51-69
EPL 0-15%
LY30 0-8

Once the bladder temperature reaches 36.5^{o} C during rewarming on cardiopulmonary bypass, obtain the following labs: TEG with heparinase, PT, INR, fibrinogen and platelet count.

1. If the R time and INR is elevated, consider transfusing FFP as below. If the R time is normal, but the INR is elevated and there is microvascular bleeding once the temperature has normalized, transfusion of FFP can still be considered.

a. 8 < R < 11 (mins) → 1 U FFP
b. 11 < R < 14 (mins) → 2 U FFP
c. 14 ≤ R (mins) → 4 U FFP

2. If the α angle and fibrinogen is decreased, consider transfusing cryoprecipitate as below. If the α angle is normal, but the fibrinogen is still decreased and there is microvascular bleeding once the temperature has normalized, transfusion of cryoprecipitate can still be considered.

a. Angle < 45^{o} → 10 U cryoprecipitate

3. If the Max Amplitude (MA) and platelet count is decreased, consider transfusing platelets as below. If the MA is normal, but the platelet count is decreased and there is microvascular bleeding once the temperature has normalized, transfusion of platelets can still be considered.

a. 46 ≤ MA < 51 (mm) → 1 U Platelets
b. 40 ≤ MA < 46 (mm) → 2 U Platelets
c. MA < 40 (mm) → 2-3 U Platelets

4. If the LY30 is elevated at greater than 8%, consider the addition of antifibrinolytic therapy with aminocaproic acid infusion