Heparin-Free Lung Transplantation on Venovenous Extracorporeal Membrane Oxygenation Bridge

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Extracorporeal membrane oxygenation (ECMO) bridge to lung transplantation (LuTX) exposes the patients to a high risk of perioperative bleeding secondary to systemic anticoagulation and coagulation factors deficiency. With this case series, we propose innovative "no-heparin" management of ECMO-bridge support during LuTX, based upon 1) control heparin resistance with antithrombin III in the preoperative period; 2) relying upon a fully functional, brand new heparinized ECMO circuit; 3) completely avoiding perioperative heparin; 4) hampering fibrinolysis with tranexamic acid; and 5) limiting venoarterial (VA) ECMO escalation, and the following need for full anticoagulation. Following the application of this new approach, we carried out three challenging clinical cases of bilateral ECMO-bridged LuTX effectively, with limited intraoperative blood requirement and no major postoperative bleeding or thromboembolic events. Of note, two of them had an extremely high risk for hemorrhage due to complete right lung anatomic derangement in case number 2 and surgical adhesion following first LuTX in case number 3, while for the case number 1, no blood products were administered during surgery. Despite the limited patient population, such an approach relies on a strong rationale and may be beneficial for managing ECMO bridging to LuTX. Prospective studies are necessary to confirm the validity of our strategy. ***ASAIO Journal*** **2021; XX;00–00**

Key Words: lung transplantation, extracorporeal membrane oxygenation, heparin, case series, extracorporeal membrane oxygenation-bridge

Extracorporeal membrane oxygenation (ECMO) is a possible strategy for bridging critically ill patients with end-stage respiratory failure to lung transplantation (LuTX) while minimizing pretransplant deconditioning.[1–3] The management of anticoagulation necessary to perform ECMO during LuTX is cumbersome. On the one hand, full anticoagulation prolonged during surgery may lead to life-threatening hemorrhage with the need for copious blood product administration, which is associated with early graft dysfunction.[4] Conversely, thromboembolic complications may occur due to platelets' activation and coagulation factors following blood contact with artificial surfaces[5] if no anticoagulation strategy is pursued.

Hereby, we describe three successful consecutive cases of venovenous (VV) ECMO bridging to LuTX managed without systemic anticoagulation. Our approach's fundamental principles are quickly reversible systemic anticoagulation and advanced daily monitoring of anticoagulation efficacy, hemolysis, and biochemistry to check the coagulation system activation (Figure 1). Prevention of heparin resistance is achieved by antithrombin III (ATIII) supplementation before and during surgery. Anticoagulation is interrupted a few hours ahead and up to 24 hours after surgery to limit intraoperative blood losses and blood product administration. Fresh frozen plasma and platelet administration are guided by point-of-care thromboelastography, while tranexamic acid and fibrinogen are supplemented whenever necessary to avoid consumption coagulopathy. Intraoperative ECMO blood flow (BF) is increased while monitoring drainage pressures to minimize platelet shear stress activation. Right ventricular inotropic support and prevention or treatment of pulmonary artery hypertension is carried out to avoid the need for venoarterial (VA) ECMO shift.

Case Reports

Recipients and donors' characteristics are illustrated in Table 1. Perioperative ECMO settings, ventilator parameters, and coagulation tests are shown in Table 2.

Case Number 1

A 28 year old (y/o) male with cystic fibrosis was admitted to the hospital with pneumonia, septic shock, and acute hypoxic-hypercapnic respiratory failure requiring intensive

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Timing		Management	Rationale
ICU		UFH infusion to maintain aPTT 1.5 to 2	Obtain reliable monitoring and quickly reversible anticoagulation
		Circuit Exchange if over 48h: D-dimer increase by 100% (levels > 30000ng/mL) & Platelets count decrease by 50% & Fibrinogen decrease by 33% Or D-dimer increase over 50000ng/mL & Platelets count below 50 *1000/mL or Fibrinogen level below 150mg/dL	Prevent hemorrhagic events secondary to coagulation activation and avoid ECMO circuit malfunctioning
		Maintain antithrombin activity > 60%	Avoid heparin resistance
Before LuTX		Interrupt UFH infusion at least 2 hours ahead of surgery	Minimize intraoperative bleeding
		Supplement ATIII if ATIII activity < 60%	Prevent ATIII consumption and dilution
Intra-operative	Hemodynamics	Monitor SVO_2, PA, wedge pressure and TEE	Monitor RV and LV function
		Increase RV inotropism (adrenaline) and/or decrease RV afterload (inhaled NO)	Avoid right heart failure thus avoiding VA - ECMO support
	ECMO settings	Maintain ECMO drainage pressure < 80mmHg	Avoid hemolysis
		Increase ECMO BF >4 L/min (compatibly with ECMO drainage pressures)	Avoid platelets shear stress & ensure adequate O_2 delivery
		Increase ECMO GF to obtain normocapnia	Allow protective lung ventilation TV < 4mL/kg on the newly implanted graft & avoid increase in PA pressure
	Coagulation monitoring and blood components	PRBC transfusion if Hb < 10 g/dL	Ensure adequate O_2 delivery
		FFP and/or Platelets transfusion according to POC viscoelastic coagulation monitoring	Maintain coagulation system homeostasis
		Infuse 5% albumin diluted in balanced crystalloids	Avoid hyperchloremia thus decreasing metabolic acidosis
		Supplement 2 g Fibrinogen if plasma levels decrease below 150 mg/dL	Avoid hypocoagulability
		Administer 1g Tranexamic Acid (before fibrinogen administration according to lysis parameters at POC)	Prevent coagulation factors consumption
Post-operative		Avoid full-anticoagulation up to 48h postoperatively	Avoid post-operative bleeding
		If no bleeding detected, provide thromboprophylaxis	Avoid post-operative thromboembolic events
		Perform early gas-off trial	Achieve early ECMO interruption
		Monitor COHb, Haptoglobin and FreeHb	Detect hemolysis

Figure 1. Perioperative ECMO management. aPTT, activated partial thromboplastin time; ATIII, antithrombin III; BF, blood flow; COHb, carboxyhemoglobin; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; GF, gas flow; Hb, hemoglobin; ICU, intensive care unit; LuTX, lung transplantation; LV, left ventricular; NO, nitric oxide; PA, pulmonary artery; POC, point of care; PRBCs, packed red blood cells; RV, right ventricular; SVO_2, mixed venous blood hemoglobin saturation of oxygen; TEE, transesophageal echocardiography; TV, tidal volume; UFH, unfractionated heparin; VA, venoarterial.

care unit (ICU) admission and invasive mechanical ventilation (Figure 2A). Preexisting poor lung function and copious secretions did not allow protective ventilation. Thus, VV ECMO (femoro-femoral cannulation, 23 Fr [Bio-Medicus NextGen; Medtronic, Minneapolis, MN, USA] and 25 Fr [HLS Cannulae; Maquet, Solna, Sweden], heparinized cannulas [CardioHelp, Maquet, Solna, Sweden]) was instituted, with a BF rate 3.7 L/min, sweep gas flow (GF) 4 L/min, and the fraction of oxygen at the membrane lung (FiO_2ML) 70%. Extracorporeal membrane oxygenation support (BF 3.5 L/min, GF 4 L/min, FiO_2ML 40%) allowed extubation after 3 days and switch to noninvasive ventilation and ECMO. To maintain therapeutic patient-to-normal clotting time activated partial thromboplastin time ratio (aPTTr) between 1.5 and 2.0, unfractionated heparin infusion was progressively increased from 17 to 28 IU/kg/hr, and ATIII was supplemented to maintain normal plasmatic activity. Despite this, an ECMO circuit exchange was necessary after 3 days due to consumption coagulopathy. Since the respiratory function did not improve, the patient was listed for LuTX on national urgency 3 days after ICU admission, and a blood group and size-matched organ became available 3 days later. We stopped unfractionated heparin infusion 3 hours before surgery and administered tranexamic acid (1gr) at the skin incision. The preoperative kaolin-activated thromboelastography

Table 1. Patients Characteristics

	Case No. 1	Case No. 2	Case No. 3
Recipient			
Age, years	28	48	25
BMI, kg/m^2	22.9	19.3	21.3
Time on WL, days	3	9	5
LAS	53.8	81.2	74.0
FVC, %	NA	47	20
FEV1, %	49	24	25
PAP s/d (m), mm Hg	57/30 (37)	49/26 (35)	62/21 (42)
Airways bacterial colonization	*Pseudomonas aeruginosa* XDR	*P. aeruginosa*	*P. aeruginosa* XDR *Achromobacter xylosoxidans*
Pre-LuTX ICU LOS, days	8	14	7
VV ECMO bridge duration, days	7	12	6
Pre-LuTX IMV duration, days	3	5	2
Donor			
Cause of death	Trauma	CVA	Trauma
PaO_2/FiO_2	630	564	490
Mechanical ventilation, days	6	2	2
Oto score*	2	10	5
Age/sex	29/male	28/female	19/male
Smoking history	2 pack/year	2.5 pack/year	5 pack/year
Secretions	++	+	+
CXR	1 lobe opacity	>1 lobe opacity	>1 lobe opacity
Cold ischemia time, minutes			
1st lung	204	451	256
2nd lung	379	641	450
Intraoperative			
Surgery duration, minutes	457	558	555
Warm ischemia time, minutes			
1st lung	96	57	75
2nd lung	71	78	55
Estimated blood loss, ml	700	3,700	2,800
Crystalloids, ml	800	1,500	1,500
5% albumin, ml	1,500	4,200	5,000
PRBC, ml	0	2,500	1,250
FFP, ml	0	2,000	0
Platelets, ml	0	0	0
Cell saver, ml	0	0	990
Postoperative			
Post-LuTX ICU LOS, days	2	3	4
Post-LuTX hospital LOS, days	28	19	19
Acute rejection	No	No	No
Post-LuTX respiratory function			
1st month FEV1/FVC, %	83/97	60/67	48/54
3rd month FEV1/FVC, %	89/80	78/75	61/61
6th month FEV1/FVC, %	99/92	82/86	76/74
Survival†, days	428	217	261

*See Oto T, Levvey BJ, Whitford H, *et al*: Feasibility and utility of a lung donor score: Correlation with early post-transplant outcomes. *Ann Thorac Surg* 83: 257–263, 2007.

†Survival on September 30, 2020.

BMI, body mass index; CVA, cardiovascular accident; CXR, chest radiograph; FEV1, forced expiratory volume in 1 second; FFP, fresh frozen plasma; FVC, forced vital capacity; ICU, intensive care unit; IMV, invasive mechanical ventilation; LAS, lung allocation score; LOS, length of stay; LuTX, lung transplantation; NA, not available; PaO_2/FiO_2, ratio of partial pressure of oxygen to fraction of inspired oxygen; PAP s/d (m), systolic, diastolic, and mean pulmonary artery pressure; PRBCs, packed red blood cells; VV ECMO, venovenous extracorporeal membrane oxygenation; WL, waiting list; XDR, extensively drug-resistant.

showed normal coagulation function (*i.e.*, R-time 3.7 minutes, K 1.2 minutes, LY-30 0.0), except for a slight reduction in clot strength (*i.e.*, maximum amplitude 30.6 mm, α-angle 34.1°). Throughout the sequential bilateral LuTX procedure, the ECMO circuit was maintained, and support was increased (BF 4.2 L/min, GF 10 L/min, FiO_2ML 100%). No blood product transfusion was necessary during surgery (Table 1).

At ICU readmission, the lung graft showed proper function: the respiratory system's compliance was 66 ml/cm H_2O with ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of 420 mm Hg (without any ECMO support, GF = 0 L/min). Accordingly, unfractionated heparin infusion was not restarted, and ECMO support was removed just after ICU admission. The patient was then extubated during the first postoperative day and transferred to the ward the following day. No thrombotic complications were observed in the postoperative period. At the time of hospital discharge, 28 days after LuTX, forced expiratory volume in 1 second and forced vital capacity were 78% and 73%, respectively, and the patient walked 570 mt at the 6-minute walking test with an average peripheral oxygen saturation (SpO_2) of 98%.

Case Number 2

A 48 y/o female patient enlisted for LuTX for idiopathic panacinar emphysema and bronchiectasis (with right lung collapse and major tracheal deviation) (Figure 2B) was admitted to the ICU for H_1N_1 influenza and, after failing a noninvasive

Table 2. Preoperative and Postoperative Respiratory and Coagulation Function Parameters

	1 Hour Before LuTX			8 Hours After ICU Admission		
Patient	1	2	3	1	2	3
ECMO BF (L/min)	2.5	2.5	2.8	2.5	2.9	3.5
ECMO GF (L/min)	3	3	7.5	3	2	2.0
FiO_2ML, %	30	55	35	21	40	35
Delta pTM, mm Hg	11	10	16	13	12	18
Natural lung ventilation, mode	NIV	NIV	NIV	PSV	PSV	PCV
RR, bpm	22	17	27	14	20	10
Pplat, cm H_2O	18	26	26	18	22	18
PEEP, cm H_2O	8	5	6	8	12	10
TV, ml	380	420	320	600	400	400
FiO_2NL, %	40	40	30	40	40	35
$PaCO_2$, mm Hg	45	42	38	42	37	34
PaO_2, mm Hg	71	72	76	138	136	84
Hb, g/dl	10.3	9.9	9.9	9.6	9.8	9.1
Platelets, 1,000/mm^3	177	315	142	179	126	75
ATIII activity, %	91	56	73	82	79	62
INR	1.15	1.08	1.01	1.19	1.15	1.19
aPTT ratio	1.43	1.03	1.08	0.9	0.9	0.95
Fibrinogen, g/dl	291	211	372	287	208	183
D-dimer, ng/ml	1,934	5,275	4,681	5,475	1,351	2,644
COHb, %	0.7	0.9	0.9	1.5	1.2	0.9
Haptoglobin, mg/dl	71	127	156	NA	61	NA

aPTT, activated partial thromboplastin time; ATIII, antithrombin III; bpm, breaths per minute; COHb, carboxyhemoglobin; ECMO BF, extracorporeal membrane oxygenation blood flow; ECMO GF, extracorporeal membrane oxygenation gas flow; FiO_2ML, fraction of oxygen at the membrane lung; FiO_2NL, natural lung fraction of oxygen; Hb, hemoglobin; ICU, intensive care unit; INR, international normalized ratio; LuTX, lung transplantation; NA, not available; NIV, non invasive ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PCV, pressure controlled ventilation; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; PSV, pressure support ventilation; pTM, transmembrane pressure; RR, respiratory rate; TV, tidal volume.

ventilation trial, she was intubated. Mechanical ventilation management was complicated due to poor patient-ventilator interaction and recurrent airway obstructions due to secretions (see Figure S1, Additional Results, Online Supplement, http://links.lww.com/ASAIO/A595). Thus, we commenced low flow extracorporeal CO_2 removal[6] (ProLUNG; Estor, Pero, Italy) (13 Fr double-lumen femoral cannula) to reduce the patient's ventilatory load, facilitate endotracheal tube removal, and allow efficacious secretions clearance. This strategy allowed rapid patient extubation to noninvasive ventilation or high flow nasal cannula. Unfortunately, on the 4th day after ICU admission, the patient was reintubated for rebellious agitation. Due to the persistence of hypoxic-hypercapnic respiratory failure (PaO_2/FiO_2 126 mm Hg, arterial partial pressure of carbon dioxide 60 mm Hg), VV

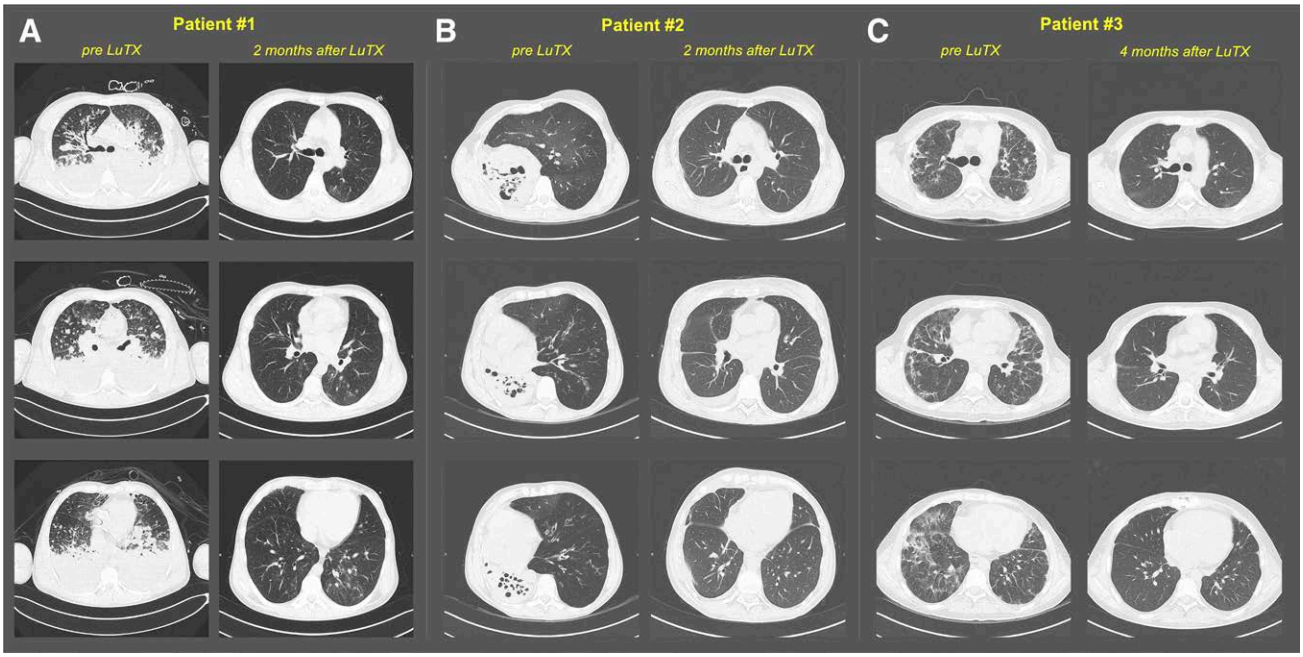

Figure 2. Patients' lung CT scans. Preoperative and postoperative CT scans of case numbers 1, 2, and 3. CT, computed tomography; LuTX, lung transplantation.

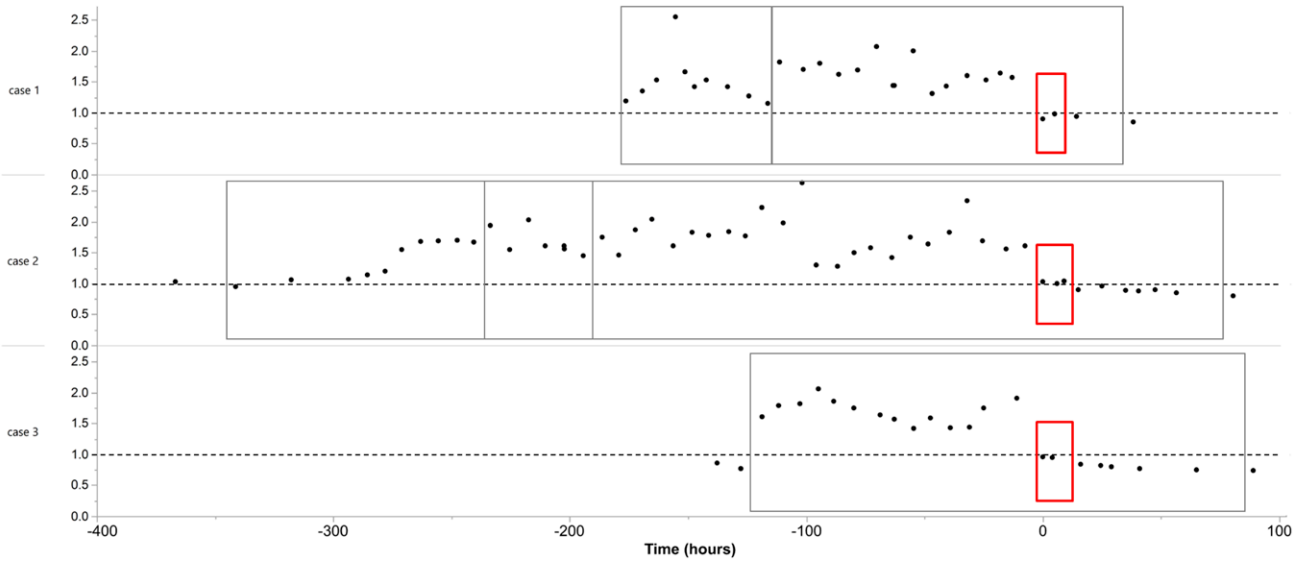

Figure 3. Activated partial thromboplastin time ratio changes over time. Time zero represent beginning of surgery. Light gray boxes represent single circuits usage, black red boxes represent surgery time.

ECMO (femoro-femoral cannulation, 21 Fr and 23 Fr outer diameter, heparinized cannulas) was initiated (BF 3.4 L/min, GF 4 L/min, FiO_2ML 70%) and thus, the patient was upgraded as urgent LuTX case. On ICU day 7, she was extubated again and maintained on awake ECMO bridge to transplantation (BF 2.5 L/min, GF 3 L/min, FiO_2ML 50%). Unfractionated heparin infusion was titrated between 28 and 33 IU/kg/hr to maintain the aPTTr between 1.5 and 2.0, while 5,000 IU ATIII (over 9 days) were administered to maintain ATIII activity above 70%. While awaiting LuTX, on the 5th and 8th day after ECMO initiation, two coagulopathy episodes required circuit substitution (Figure 3). On the 14th day after ICU admission (9th day on ECMO), a compatible organ became available. We stopped unfractionated heparin infusion 4 hours before surgery. Preoperative kaolin-activated thromboelastography showed normal coagulation function (*i.e.*, R-time 4.3 minutes, α-angle 65.0°, K 1.2 minutes, maximum amplitude 73.6 mm, LY-30 0.0 mm). During LuTX, the ECMO circuit and cannulation were not modified, but extracorporeal support was increased to BF 3.2 L/min, GF 4.5 L/min at 100% FiO_2ML. As expected, the surgical procedure was complicated by acute bleeding (>2,500 ml) due to lysis of firm pleural adhesions during right lung pneumonectomy, which required high-volume fluid and blood components replacement (Table 1). At ICU readmission, the graft showed proper function: the respiratory system's compliance was 50 ml/cm H_2O and PaO_2/FiO_2 340 mm Hg at ECMO gas-off. Heparin infusion was not restarted, and ECMO was removed on postoperative day 1. The patient was extubated on the second postoperative day and discharged from ICU on the third postoperative day. She was discharged from hospital on the 19th postoperative day and with forced expiratory volume in 1 second and forced vital capacity were 52% and 50%, performing 360 mt at the 6-minute walking test with average SpO_2 of 96%.

Case Number 3

A 25 y/o male cystic fibrosis patient underwent bilateral LuTX for end-stage respiratory insufficiency and recurrent respiratory infections (Figure 2C). Despite an uneventful hospital course, he developed antibody-mediated rejection with graft function loss in the immediate post-transplant period complicated by an episode of acute fibrinoid organizing pneumonia 14 months after transplantation. The progressive worsening of hypoxemic respiratory insufficiency led to hospital and ICU admission and invasive mechanical ventilation initiation. The patient was then enlisted for lung retransplantation on a national urgency, and VV ECMO (femoro-femoral cannulation, 23 Fr and 25 Fr outer diameter, heparinized cannulas) was instituted (BF 3.8 L/min, GF 3.0 L/min, 50% FiO_2ML). Unfractionated heparin infusion was titrated according to the Institutional ICU anticoagulation protocol (Figure 1). One day after ECMO start, the patient was extubated. During awake ECMO bridge (BF 3.8 L/min, GF 5.5 L/min) to LuTX, spontaneous breathing was supported by either high flow nasal cannula or noninvasive ventilation. On the 5th day after ECMO initiation, a compatible graft became available. Heparin infusion was interrupted 2 hours before surgery initiation, and the preoperative kaolin-activated thromboelastography showed normal coagulation function (*i.e.*, R-time 6.2 minutes, α-angle 51.4°, K 1.3 minutes, maximum amplitude 68.1 mm, LY-30 0.0 mm). Sequential bilateral LuTX was performed. Intraoperatively, ECMO support was increased to BF 4.0 L/min, GF 10 L/min at 100% FiO_2ML. Throughout the whole surgery, to avoid VA ECMO escalation, inhaled nitric oxide was used up to 40 part per million in the setting of increased pulmonary pressure and transesophageal echocardiographic evidence of right ventricular dilatation. During the surgical procedure, we measured ATIII activity (<70%), and thus 1,000 IU of ATIII was administered. The graft showed immediately good lung mechanics (compliance of the respiratory system was 40 ml/cm H_2O) and imaging at the chest radiograph. On the first postoperative day, lung mechanics and graft gas exchange were acceptable (PaO_2/FiO_2 261 mm Hg at ECMO gas-off); thus, the patient was weaned from ECMO, then from invasive mechanical ventilation. Four units of packed red blood cells and 500 ml of fresh frozen plasma were transfused along the first 2 postoperative days, due to blood loss from

drainages leading to hemoglobin < 10 mg/dl and initial signs of coagulopathy at thromboelastography, without overt hemorrhagic shock. At hospital discharge, occurred on the 19th postoperative day, no thromboembolic complications were observed, forced expiratory volume in 1 second and forced vital capacity were 61% and 60%, and the patient performed 557 mt at the 6-minute walking test with average SpO_2 of 97%.

Discussion

With this case series, we describe the successful perioperative course of three VV ECMO-bridged LuTX patients and propose an innovative "no-heparin" perioperative management of ECMO-bridge support during LuTX. With this approach, we could conduct three challenging clinical cases effectively, with limited blood requirements and no major postoperative bleeding or thromboembolic events. Of note, two patients (numbers 2 and 3) had an extremely high risk of hemorrhage for anatomical or surgical procedural reasons, while patient number 1 did not need any blood product transfusion during surgery. At the time of this writing, all three patients are alive, did not show any sign of rejection, and have normal lung functionality.

We previously reported an incidence of hemorrhagic complications requiring more than ten packed red blood cells units intraoperatively or within the first 24 postoperative hours, in about 30% of LuTX in ECMO-bridge patients,[7] with the need of an intraoperative upgrade to VA ECMO (and thus escalation to full anticoagulation) in seven out of 16 procedures. Moreover, in a cohort of cystic fibrosis patients undergoing LuTX, we observed that ECMO-bridged patients had higher intraoperative and postoperative transfusion requirements than non-ECMO-bridged patients and more frequent surgical revision due to bleeding complications (23% *vs.* 3%).[8] By further reviewing all patients' clinical charts requiring VV ECMO bridge to LuTX at our institution (2011 to 2018 [n = 24]), we observed an average intraoperative transfusion requirement of 11 ± 7 units of packed red blood cells, 10 ± 10 units of fresh frozen plasma, and 3 ± 5 platelets pool.

In light of these data, with the support of the Institutional hematologists, we developed a practical protocol for managing anticoagulation in patients bridged with ECMO to LuTX (Figure 1). In this clinical scenario, the overall rationale is that with a VV ECMO lung support, the hemorrhagic risk far outweighs the thrombotic risk. Thus, we rely upon a fully functional heparinized ECMO circuit (*i.e.*, polymethylpentene hollow-fiber oxygenator, heparin-coated cannulas, and circuit), avoid intraoperative heparin, and possibly limit escalation to VA ECMO and the following need for full anticoagulation. Such an approach should theoretically allow a prompt return to the coagulative system's normal function with reduced intraoperative bleeding events.

Off-pump LuTX patients are affected by a hypercoagulable status despite a pronounced prolongation of the conventional coagulation parameters due to a low level of critical endogenous anticoagulant proteins following hemodilution[9] and, during ECMO support, to ATIII consumption. Accordingly, patients undergoing LuTX are exposed to a high risk of thromboembolism.[10] With our approach, this imbalance of coagulation system toward thromboembolism and consumption coagulopathy is contrasted by preoperative supplementation of fibrinogen and ATIII, prophylactic tranexamic acid, and ECMO circuit substitution whenever early signs of coagulation system activation are detected. Indeed, a fully heparin-coated ECMO circuitry is known to provide sufficient antithrombotic function for limited periods, up to 24–48 hours.[11] Moreover, ECMO BF should be increased with the aim of 1) obtaining controlled reperfusion by lowering pulmonary artery pressure and thus endothelium shear stress[12] and 2) limiting shear stress associated coagulopathy.[13] Sweep GF and membrane lung fraction of inspired oxygen are titrated to permit protective graft ventilation while ensuring adequate tissue oxygen delivery and avoiding hypercapnia. Additionally, perioperative thromboelastography-guided coagulation monitoring was adopted[14] to diagnose and target ongoing coagulation alterations accurately. Finally, avoiding intraoperative switch to VA ECMO is crucial in this setting, since implementing central VA cannulation implies full anticoagulation and a high risk of hemorrhage. Of note, at our institution, cell blood savers are not usually utilized for patients with cystic fibrosis or bronchiectasic diseases, due to the possible contamination of saved blood from the surgical field, which is heavily soiled by the receiver's secretions. We use cell blood savers only for patients with limited available compatible blood components, such as patients number 3, which had multiple blood incompatibilities due to the previous LuTX and multiple blood transfusions.

In agreement with the Extracorporeal Life Support Organization guidelines, the most common anticoagulation strategy during ECMO bridging to LuTX implies unfractionated heparin (UFH) continuous infusion targeting either 40–60 seconds aPTTr[1] or 160–180 activated clotting time measured twice a day.[3] In contrast, Gratz *et al.*[15] recently described the use of low molecular weight heparin (0.8 mg/kg/day) to manage the perioperative phase of LuTX patients requiring extracorporeal support. We chose unfractionated heparin since it has a much shorter half-life, and its effects can be easily measured by point-of-care coagulation monitoring (*i.e.*, aPTT, thromboelastography).

In a previous article,[8] we described our institution's clinical experience with 13 cystic fibrosis patients bridged to LUTX with preoperative VV ECMO. The proposed protocol was not employed, and the median dosage of intraoperative unfractionated heparin was 23.0 UI/kg/hr (17.6–26.4 UI/kg/hr). In five patients (38%), upgrade to central VA ECMO was implemented for hemodynamic failure. Intraoperative and postoperative blood component usage was 2,995 ml (1,425–7,077 ml) and 2,565 ml (855–5,265 ml), respectively. Invasive mechanical ventilation, ICU, and hospital length of stay lasted 4 days (1–22 days), 6 days (4–24 days), and 35 days (20–51 days). Survival at follow-up (median time 1,255 days [849–1,881 days]) was 77%. Despite the small number of patients—and thus, the uselessness of any statistical analyses—the advantages upon blood component usage of the proposed protocol are evident. Similarly, the length of invasive mechanical ventilation, ICU, and hospital length of stay appear to be shorter in patients who are managed following this no-heparin protocol; however, the timing of follow-up is different, and thus any reasoning on survival is preposterous.

Conclusions

We propose a "no-heparin" management of ECMO-bridge support during LuTX, based upon 1) control heparin resistance

with ATIII in the preoperative period; 2) relying upon a fully functional, brand new heparinized ECMO circuit; 3) completely avoiding perioperative heparin; 4) hampering fibrinolysis with tranexamic acid; and 5) limiting VA ECMO escalation. Following the application of this new approach, we carried out three challenging clinical cases of bilateral ECMO-bridged LuTX effectively, with limited intraoperative blood requirement and no major postoperative bleeding or thromboembolic events. We acknowledge that prospective studies on larger patient populations are necessary to confirm the validity of our strategy; however, we believe that the proposed approach relies on a strong rationale and may be beneficial for managing ECMO bridging to LuTX.

References

1. Javidfar J, Brodie D, Iribarne A, *et al*: Extracorporeal membrane oxygenation as a bridge to lung transplantation and recovery. *J Thorac Cardiovasc Surg* 144: 716–721, 2012.
2. Nosotti M, Rosso L, Tosi D, *et al*: Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. *Interact Cardiovasc Thorac Surg* 16: 55–59, 2013.
3. Fuehner T, Kuehn C, Hadem J, *et al*: Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med* 185: 763–768, 2012.
4. Weber D, Cottini SR, Locher P, *et al*: Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. *Perioper Med (Lond)* 2: 20, 2013.
5. Protti A, L'Acqua C, Panigada M: The delicate balance between pro-(risk of thrombosis) and anti-(risk of bleeding) coagulation during extracorporeal membrane oxygenation. *Ann Transl Med* 4: 139, 2016.
6. Grasselli G, Castagna L, Bottino N, *et al*: Practical clinical application of an extracorporeal carbon dioxide removal system in acute respiratory distress syndrome and acute on chronic respiratory failure. *ASAIO J* 66: 691–697, 2020.
7. Crotti S, Iotti GA, Lissoni A, *et al*: Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcomes. *Chest* 144: 1018–1025, 2013.
8. Scaravilli V, Morlacchi LC, Merrino A, *et al*: Intraoperative extracorporeal membrane oxygenation for lung transplantation in cystic fibrosis patients: Predictors and impact on outcome. *J Cyst Fibros* 19: 659–665, 2020.
9. Ruitenbeek K, Hugenholtz GC, Adelmeijer J, *et al*: Development of a hypercoagulable status in patients undergoing off-pump lung transplantation despite prolonged conventional coagulation tests. *Am J Respir Crit Care Med* 191: 230–233, 2015.
10. Sáez-Giménez B, Berastegui C, Sintes H, *et al*: Prophylaxis with enoxaparin for prevention of venous thromboembolism after lung transplantation: A retrospective study. *Transpl Int* 30: 1266–1274, 2017.
11. Fina D, Matteucci M, Jiritano F, *et al*: Extracorporeal membrane oxygenation without therapeutic anticoagulation in adults: A systematic review of the current literature. *Int J Artif Organs* 43: 570–578, 2020.
12. Hoetzenecker K, Benazzo A, Stork T, *et al*; Vienna Lung Transplant Group: Bilateral lung transplantation on intraoperative extracorporeal membrane oxygenator: An observational study. *J Thorac Cardiovasc Surg* 160: 320–327.e1, 2020.
13. Ki KK, Passmore MR, Chan CHH, *et al*: Low flow rate alters haemostatic parameters in an ex-vivo extracorporeal membrane oxygenation circuit. *Intensive Care Med Exp* 7: 51, 2019.
14. Smith I, Pearse BL, Faulke DJ, *et al*: Targeted bleeding management reduces the requirements for blood component therapy in lung transplant recipients. *J Cardiothorac Vasc Anesth* 31: 426–433, 2017.
15. Gratz J, Pausch A, Schaden E, *et al*: Low molecular weight heparin versus unfractioned heparin for anticoagulation during perioperative extracorporeal membrane oxygenation: A single center experience in 102 lung transplant patients. *Artif Organs* 44: 638–646, 2020.