Initial experience and outcomes with a hybrid extracorporeal membrane oxygenation and cardiopulmonary bypass circuit for lung transplantation

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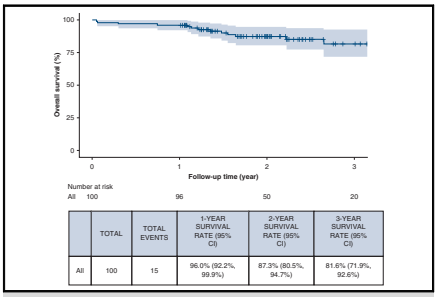
ABSTRACT

Background: The utilization of extracorporeal life support (ECLS) for intraoperative support during lung transplantation has increased over the past decade. Although veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has recently emerged as the preferred modality over cardiopulmonary bypass (CPB), many centers continue to use both forms of ECLS during lung transplantation. Our novel hybrid VA-ECMO/CPB circuit allows for seamless transition from VA-ECMO to CPB at a significant cost savings compared to a standalone VA-ECMO circuit. This study describes our initial experience and outcomes in the first 100 bilateral lung transplantations using this novel hybrid VA-ECMO/CPB circuit.

Methods: Medical records from September 2017 to May 2021 of the first 100 consecutive patients undergoing bilateral lung transplantation with intraoperative hybrid VA-ECMO support were examined retrospectively. We excluded patients with single lung transplants, retransplantations, preoperative ECLS bridging, and veno-venous (VV) ECMO and those supported with CPB only. Perioperative recipient, anesthetic, perfusion variables, and outcomes were assessed.

Results: Of the 100 patients supported with VA-ECMO, 19 were converted intraoperatively to CPB. Right ventricular dysfunction was seen in 37% of patients, and the median mean pulmonary artery pressure was 28 mm Hg. No oxygenator clotting was observed with a median heparin dose of 13,000 units in the VA-ECMO group. Primary graft dysfunction grade 3 at 72 hours was observed in 10.1% of all patients and observed 1-year mortality was 4%.

Conclusions: The use of a hybrid VA-ECMO/CPB circuit in our institution allows for rapid conversion to CPB with acceptable outcomes across a diverse recipient group at a significantly reduced cost compared to standalone VA-ECMO circuits. (JTCVS Open 2023;16:1029-37)



	TOTAL	TOTAL EVENTS	1-YEAR SURVIVAL RATE (95% CI)	2-YEAR SURVIVAL RATE (95% CI)	3-YEAR SURVIVAL RATE (95% CI)
All	100	15	96.0% (92.2%, 99.9%)	87.3% (80.5%, 94.7%)	81.6% (71.9%, 92.6%)

Outcomes across entire cohort supported with a hybrid ECMO/CPB circuit.

CENTRAL MESSAGE

In this retrospective study, intraoperative support with a hybrid VA-ECMO/CPB circuit in lung transplantation resulted in excellent perioperative and short-term outcomes with significant cost savings.

PERSPECTIVE

Although extracorporeal membrane oxygenation (ECMO) has recently emerged as the preferred modality for intraoperative support in lung transplantation, cardiopulmonary bypass (CPB) is still used by many centers. Our hybrid ECMO/CPB circuit allowed for an ECMO approach with CPB backup, with excellent outcomes across a diverse end-stage lung disease recipient group at a significantly reduced cost per circuit.

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Abbreviations and Acronyms

ACT = activated clotting time
CPB = cardiopulmonary bypass
ECLS = extracorporeal life support
ECMO = extracorporeal membrane oxygenation
ESLD = end-stage lung disease
ICU = intensive care unit
ISHLT = International Society for Heart and Lung Transplantation
MDT = multidisciplinary team
PAP = pulmonary artery pressure
PGD = primary graft dysfunction
VA = veno-arterial
VV = veno-venous

The progressive evolution of perioperative lung transplantation management has originated from the nexus of multidisciplinary teamwork and technological advances.[1,2] Working within this multidisciplinary framework allows for multiple perspectives on a given topic, with hopes of optimizing efficiency beyond the work of a homogenous team alone. Although the definitive optimal form of extracorporeal life support (ECLS) for lung transplantation remains a matter of debate, the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for intraoperative ECLS has been associated with reduced primary graft dysfunction (PGD) and excellent outcomes across a wide range of etiologies of end-stage lung disease (ESLD).[3] Full cardiopulmonary bypass (CPB) has been used both routinely by some groups[3] and selectively by others during lung transplantation. In our practice, we use CPB in lung transplantation selectively for concomitant cardiac operations or when necessary because of such operative factors as refractory hemodynamic instability, uncontrolled hemorrhage, and inadequate surgical exposure.

Our multidisciplinary team (MDT) designed a novel hybrid ECMO-CPB circuit (Figure 1) that serves as a VA-ECMO circuit at a lower cost than a standalone ECMO circuit but allows for a rapid and simple transition to CPB if needed. We implemented an MDT protocol using this hybrid circuit focused on intraoperative VA-ECMO support for lung transplantation across a wide range of recipient comorbidities. Both the design of our hybrid circuit and the protocol for intraoperative management have been reported previously.[4,5] Here we present the data for recipient, anesthetic, perfusion, and outcome variables from the first 100 cases in which the hybrid VA- ECMO/CPB circuit was used in our practice.

METHODS

This study was designed as a single-center, retrospective, descriptive study including 125 lung transplantations performed between September 2017 and May 2021. The study was deemed exempt from Institutional Review Board review on December 28, 2020, by the Mayo Clinic's Institutional Review Board (Application 20-012878), and the study was conducted in strict compliance with the International Society for Heart and Lung Transplantation Ethics Statement.

Exclusion criteria included single lung transplantation, retransplantation, preoperative ECLS bridge to transplantation, planned ECLS of either CPB or veno-venous (VV) ECMO, and lung transplantations performed without ECLS support. One hundred patients met the inclusion criteria and received ECLS support using the hybrid VA-ECMO/CPB circuit[4] (Table 1). Data were input and managed using Research Electronic Data Capture (REDCap) hosted at the Mayo Clinic.[6,7] Follow-up of patient outcomes data extended until May 2022, at least 1 year after the final recipient in the data set.

Categorical variables were summarized as frequency (percentage), and continuous variables were reported as median (interquartile range). Missing variables from the chart are noted in the respective data tables. PGD was calculated according to the latest International Society for Heart and Lung Transplantation criteria,[8] with patients on prolonged ECMO graded according to the published Vienna group approach of PGD grade 3 classification if chest X-ray infiltrates were noted.[9] The Wilcoxon signed-rank test was used to evaluate the difference in selected continuous variables between patients with and without conversion, and the Fisher exact test was used to compare categorical variables. All tests were 2-sided, with $P < .05$ considered to indicate statistical significance. Statistical analysis was done using SAS 4.0.3 (SAS Institute).

RESULTS

A total of 100 patients who underwent bilateral lung transplantation with the hybrid VA-ECMO/CPB circuit were included in the analysis. Recipient demographic and baseline data are listed in Table 2. The cohort had a median age of 58 years (interquartile range, 23-74 years), and 45% of the patients were age ≥60 years. The majority (61%) of the patients were overweight (body mass index, 25-29.9) or

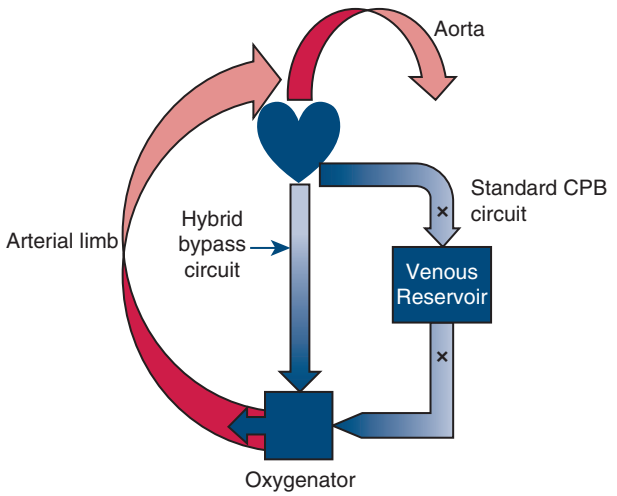

FIGURE 1. Diagram showing the hybrid bypass circuit for venoarterial extracorporeal membrane oxygenation (*ECMO*) during lung transplantation. Xs denote the clamps placed to bypass the venous reservoir for ECMO. *CPB*, Cardiopulmonary bypass. Used with permissions from Thomas and colleagues.[4]

TABLE 1. Hybrid VA ECMO-CPB circuit components

Oxygenator	Pump	Tubing	Monitoring
LivaNova Inspire 6FD	LivaNova S5	LivaNova Smart Perfusion Pack	CDI 550 inline blood gas monitor

Additional information is available from LivaNova for the oxygenator, pump, and tubing and from Terumo Cardiovascular for the CDI 550 monitor.

obese (body mass index, 30-34.9). The predominant etiology of recipient ESLD was restrictive lung disease (67%); other etiologies included obstructive disease (18%), primary pulmonary hypertension (8%), and suppurative disease (7%).

Anesthetic variables are listed in Table 3. The median intraoperative resuscitation volumes were as follows: crystalloid, 2900 mL; albumin colloid, 2000 mL; packed red blood cells, 1400 mL; fresh frozen plasma, 500 mL; and platelets, 200 mL. The median inhaled fraction of inspired oxygen value at first lung reperfusion was 58%, and the median mean pulmonary artery pressure (PAP) was 28 mm Hg. Qualitative and quantitative right ventricular assessment of function and size, as measured by preoperative echocardiography, were dysfunctional in 37% of patients, with enlargement seen in 42%.

Perfusion variables are listed in Table 4. Nineteen patients underwent conversion to CPB. The median maximum activated clotting time (ACT) in nonconverted patients was 228 seconds, with a median heparin dosage of 13,000 IU. No oxygenator clotting events were documented in the entire cohort.

TABLE 2. Patient demographic and baseline data (N = 100)

Characteristic	Value
Age at transplantation, y, median (IQR)	58.6 (23.5-74.4)
Age category, n (%)	
<60 y	55 (55.0)
60-69 y	33 (33.0)
≥70 y	12 (12.0)
Sex, n (%)	
Male	59 (59.0)
Female	41 (41.0)
BMI at time of transplantation, median (IQR)	26.8 (17.1-36.1)
BMI category, n (%)	
<20	8 (8.0)
20-24.9	31 (31.0)
25-29.9	38 (38.0)
30-34.9	21 (21.0)
≥35	2 (2.0)
LAS score, median (IQR)	44.3 (31.6-91.3)
Etiology of ESLD, n (%)	
Primary pulmonary hypertension	8 (8.0)
Restrictive	67 (67.0)
Obstructive	18 (18.0)
Suppurative	7 (7.0)

IQR, Interquartile range; *BMI*, body mass index; *LAS*, lung allocation score; *ESLD*, end-stage lung disease.

The components of the hybrid VA-ECMO/CPB circuit (Table 1) provide a significant cost savings compared to other commercial standalone VA-ECMO circuits. The relative value unit is such that approximately 20 hybrid circuits can be deployed for the cost of a single standalone traditional VA-ECMO circuit, resulting in a significant cost savings per transplantation over a standard model. The median total time on ECLS was 299.5 minutes.

Short-term and 1-year outcome data are listed in Table 5. Comorbidities examined included hemodialysis within

TABLE 3. Anesthetic variables

Variable	Value
Intraoperative crystalloid, median (IQR)	2900.0 (500.0-10,000.0)
Intraoperative colloid (albumin), median (IQR)	2000.0 (0.0-7000.0)
Intraoperative PRBC, median (IQR)	1400.0 (0.0-14,050.0)
Intraoperative FFP, median (IQR)	500.0 (0.0-6950.0)
Intraoperative platelets, median (IQR)	200.0 (0.0-3750.0)
Intraoperative cryoprecipitate, median (IQR)	0.0 (0.0-1400.0)
Intraoperative cellsaver, median (IQR)	900.0 (0.0-4950.0)
Intraoperative urine output, median (range)	1700.0 (1000.0-2250.0)
Inhaled FiO_2 at reperfusion of first lung, median (range)	58.0 (20.0-100.0)
Preoperative RV function, n (%)	
Normal	63 (63.0)
Mild dysfunction	24 (24.0)
Moderate dysfunction	6 (6.0)
Severe dysfunction	7 (7.0)
Preoperative RV size, n (%)	
Normal	58 (58.0)
Mildly enlarged	22 (22.0)
Moderately enlarged	7 (7.0)
Severely enlarged	13 (13.0)
PAP, systolic	
N-miss, n	1
mm Hg, median (IQR)	42.0 (35.0-53.8)
PAP, diastolic	
N-miss, n	1
mm Hg, median (IQR)	22.0 (17.0-27.0)
PAP, mean	
N-miss, n	1
mm Hg, median (IQR)	28.0 (24.0-36.0)

IQR, Interquartile range; *PRBC*, packed red blood cells; *FFP*, fresh frozen plasma; *FiO_2*, fraction of inspired oxygen; *RV*, right ventricle; *PAP*, pulmonary artery pressure; *N-miss*, unable to obtain data.

TABLE 4. Perfusion data

Parameter	Conversion (N = 19)	No conversion (N = 81)	Total (N = 100)	*P* value
Heparin dose, IU, median (IQR)	43,000.0 (30,500.0-54,000.0)	13,000.0 (10,000.0-16,000.0)	14,000.0 (11,000.0-21,250.0)	**<.001**
ACT minimum				.87
N-miss, n	0	1	1	
s, median (IQR)	166.0 (117.0-232.5)	161.0 (135.0-176.0)	161.0 (129.0-177.0)	
ACT maximum				**<.001**
N-miss, n	0	1	1	
s, median (IQR)	638.0 (556.0-772.5)	228.5 (198.0-272.0)	246.0 (203.0-309.0)	
Peak intraoperative lactate				.45
N-miss, n	1	2	3	
Median (IQR)	4.0 (2.9-6.1)	3.9 (2.3-5.6)	3.9 (2.5-6.0)	
Total ECLS time				**.001**
N-miss, n	0	2	2	
min, median (IQR)	359.0 (291.5-426.0)	292.0 (242.5-334.5)	299.5 (252.5-338.0)	

Bold indicates significant *P* values <.05. *IQR*, Interquartile range; *ACT*, activated clotting time; *N-miss*, unable to obtain data; *ECLS*, extracorporeal life support.

TABLE 5. Short-term and 1-year outcome data

Outcome	Value
PGD, hour 0 ECMO grade, n (%)	
Ungradable	5
0	41 (43.2)
1	15 (15.8)
2	19 (20.0)
3	20 (21.1)
PGD, hour 24 ECMO grade, n (%)	
Ungradable	5
0	35 (36.8)
1	32 (33.7)
2	13 (13.7)
3	15 (15.8)
PGD, hour 48 ECMO grade, n (%)	
Ungradable	4
0	32 (33.3)
1	35 (36.5)
2	12 (12.5)
3	17 (17.7)
PGD, hour 72 ECMO grade, n (%)	
Ungradable	1
0	39 (39.4)
1	28 (28.3)
2	22 (22.2)
3	10 (10.1)
Central vascular injury, n (%)	0 (0.0)
Peripheral vascular injury, n (%)	0 (0.0)
Hemodialysis within 7 d, n (%)	5 (5.0)
Stroke within 30 d, n (%)	2 (2.0)
Hospital length of stay, d, median (IQR)	22.5 (15.0-34.2)
30-d mortality, n (%)	2 (2.0)
1-y mortality, n (%)	4 (4.0)

PGD, Primary graft dysfunction; *ECMO*, extracorporeal membrane oxygenation; *IQR*, interquartile range.

7 days postoperatively (5%), stroke within 30 days postoperatively (2%), and central (0%) and peripheral (0%) vascular injury. PGD data are listed at times 0, 24, 48, and 72 hours, with time 0 defined at the time of arrival to the intensive care unit. PGD grade 3 at 72 hours was observed in 10.1% of patients, with 1 patient having ungradable PGD (listed as grade ECMO) at 72 hours owing to ongoing postoperative ECMO. All 100 patients were included within the 30-day mortality (2%) and 1-year mortality (4%) data sets. The median hospital length of stay was 22.5 days. Table E1 lists Kaplan-Meier estimates of overall survival, with freedom from death of 96% (95% CI, 92.2%-99.9%) at 1 year, 87.3% (95% CI 80.5%-94.7%) at 2 years, and 81.6% (95% CI, 71.9%-92.6%) at 3 years across the time-limited follow-up cohort. The overall survival curve for the entire cohort is shown in Figures 2 and 3.

DISCUSSION

VA-ECMO Versus CPB

ECLS can be used for cardiopulmonary support in lung transplant recipients throughout the entire perioperative phase of care, including bridging to transplantation and postoperative prolongation.[10] In the intraoperative setting, ECLS can be implemented for cardiopulmonary support with VA-ECMO or CPB. Single-center studies have shown improved PGD and morbidity rates when VA-ECMO is used compared to no support,[11,12] whereas a recent multicenter study reported superior off-pump results.[13] Magouliotis and colleagues[14] published a meta-analysis showing these improvements when VA-ECMO was compared to CPB, and a recent single-discipline consensus statement from the American Association for Thoracic Surgery concluded that VA-ECMO is the preferred method of intraoperative ECLS.[15] Despite these data, however, there

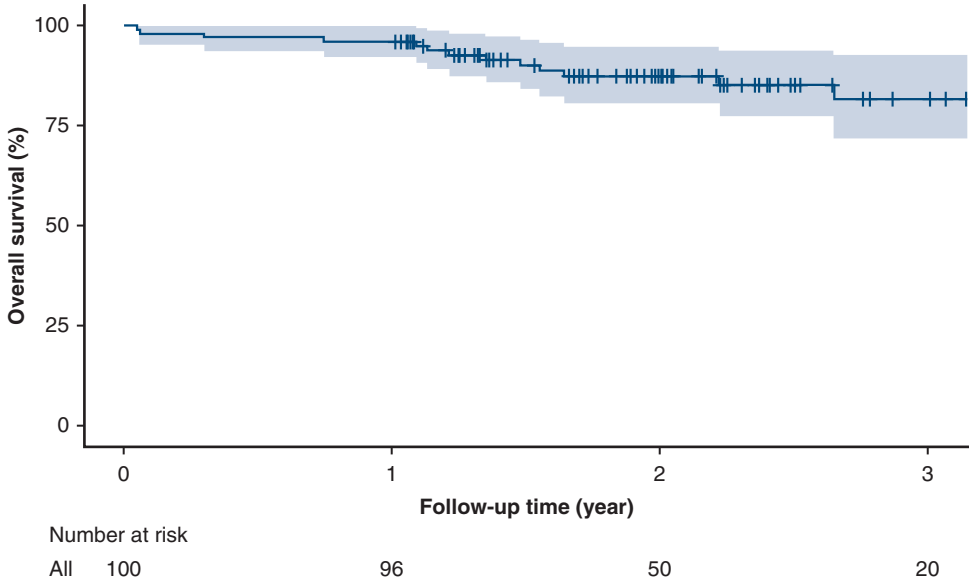

FIGURE 2. Kaplan-Meier survival curve for the entire cohort (95% confidence limits in Table E1).

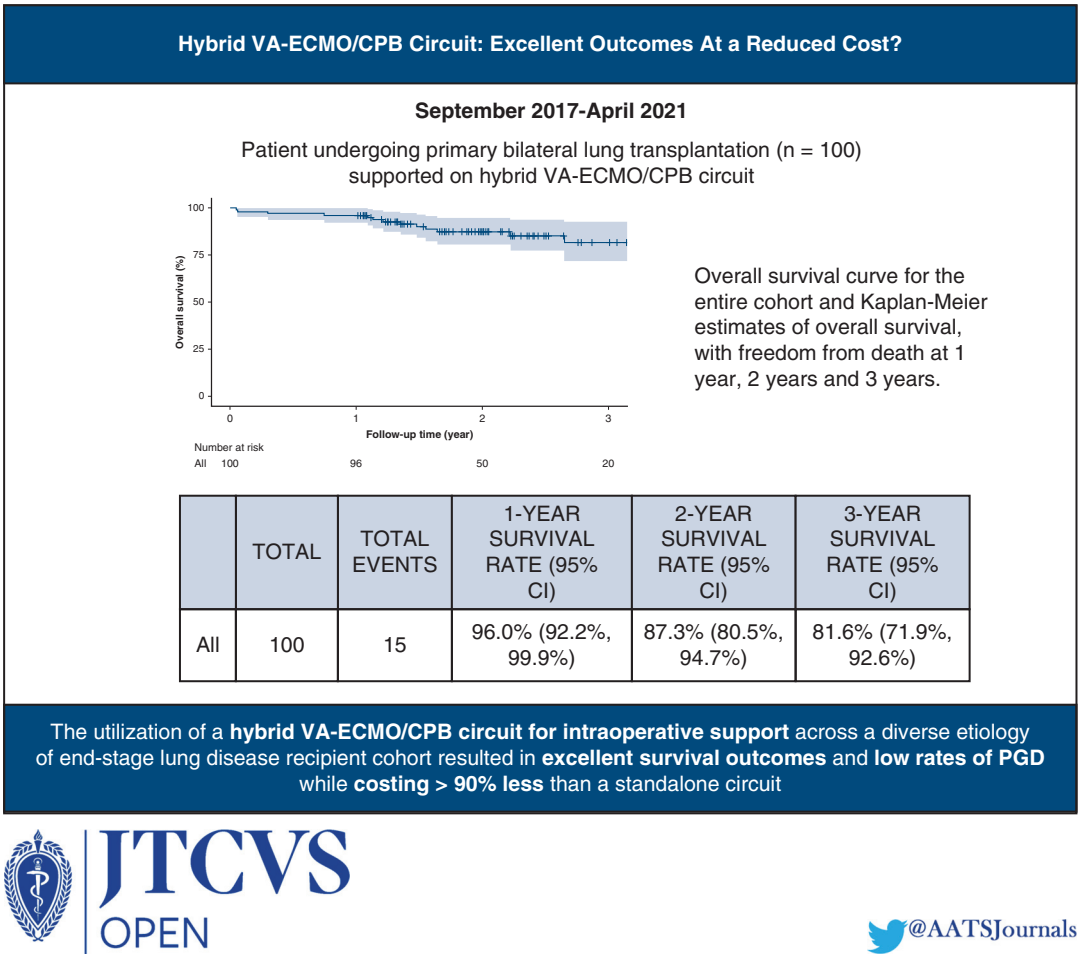

FIGURE 3. Graphical abstract. *VA-ECMO*, Veno-arterial extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass; *CI*, confidence interval.

remain significant variations in practice across different institutions regarding the choice of intraoperative ECLS support in lung transplantation. The choice of ECLS support may be driven by various factors, including surgeon experience and preference, the need for concomitant cardiac procedures, and recipient comorbidities related to primary ESLD, such as right ventricular dysfunction or elevated PAP.

Hybrid VA-ECMO/CPB Development

We designed the novel hybrid VA-ECMO/CPB circuit[4] taking both the improved outcomes data with VA-ECMO and the variability in clinical approaches among surgeons into consideration. Using a MDT-designed protocol, we have been able to successfully implement the hybrid circuit during lung transplantation, selecting the ECLS modality according to patient comorbidities.[5] This strategy was of particular importance for our recipient cohort, which had high rates of obesity, advanced age, elevated PAP, and right ventricular dysfunction. Although no data have been published examining predictors of unplanned conversion of VA-ECMO to CPB in lung transplantation, our cohort of 100 patients had 19 conversions to CPB, with 7 converting for concomitant cardiac procedures, 8 converting owing to inadequate surgical exposure, and only 4 converting secondary to hemodynamic instability. Although the impact of an MDT protocol on the rate of conversion is outside the scope of this study, our limited conversion rate for hemodynamic instability attests to the potential hypothesis that an MDT implementation protocol may have a positive impact on intraoperative maintenance of an ECMO approach across a population with significant comorbidities. Examining our outcomes, we observed a low rate of PGD grade 3 at 72 hours, excellent 1-year survival outcomes across the entire cohort, and no circuit-related complications with our anticoagulation strategy.

Fluid Resuscitation and PGD

Our previously described anesthetic management approach focuses on achievement of intraoperative cardiopulmonary stability, with incorporation of tailored strategies to attenuate the risk of PGD development.[16,17] The reported rate of PGD grade 3 of 10.1% at 72 hours along with a 1-year survival rate of 96% show that acceptable outcomes were achieved using this method of intraoperative support within our diverse recipient population. Interestingly, our patient cohort required substantial intraoperative fluid resuscitation to achieve euvolemia, which was evaluated with intraoperative transesophageal echocardiography combined with clinical assessments, including urine output, qualitative end-tidal CO_2, and hemodynamic stability.[5]

These results show a resuscitative strategy that is counter to published data regarding the impact of intraoperative fluid administration on the development of PGD.[18] Although the study from Geube and colleagues[18] included patients who underwent both off-pump and CPB support, the necessity of aggressive intraoperative resuscitation during VA-ECMO should be studied in the context of outcomes, patient stability, and target VA-ECMO flows intraoperatively.

A possible explanation for our aggressive resuscitation results is the intraoperative focus on maintaining a qualitative pulmonary arterial and systemic arterial pulsatility in the setting of high VA ECMO flow (80% of calculated cardiac output). Maintaining pulsatility requires a balance between the native cardiac output and VA ECMO flow, which can be particularly challenging intraoperatively during surgical manipulation of the heart. Correcting derangements in native cardiac output with inotropic therapy during this time may lead to increased arrythmias or dynamic outflow obstruction, whereas correcting them with vasopressor therapy alone may mask a decrease in systemic preload that eventually will lead to inadequate ECMO flow. Thus, our strategy with the foundational goal of maintaining biventricular pulsatility guided by intraoperative monitors and indices of systemic perfusion likely leads to an aggressive resuscitation.[19]

Circuit and Anticoagulation Strategies

Our previous report[4] on the design focused on modification of the CPB circuit to bypass the flow of venous blood away from the venous reservoir in the circuit, thereby minimizing the blood–air interface that is reported to increase cytokine release, coagulopathy, and blood product administration.[20] The administration of blood products intraoperatively has been associated with poor outcomes in lung transplantation,[21] and our perfusion strategy is focused on providing adequate cardiopulmonary support while minimizing heparin administration. The data to support this strategy are limited, and our approach is to aggressively measure coagulation status every 30 minutes after ECMO initiation. Despite a median ACT minimum of 161 seconds and peak of 228 seconds, no oxygenator issues were reported in the entire cohort. This anticoagulation approach is but one of many safety measures our team used during hybrid circuit design and implementation. Other measures included the use of a bubble detector for circuit shutdown in the venous (afferent) limb, frequent checking of the oxygenator for clot formation, and a rapid communication technique for conversion for CPB if needed.[4] Every 30 minutes, in addition to ACT, ongoing assessments of systemic perfusion adequacy included arterial blood gas and lactate analyses. Our data show a median peak lactate of 3.9 across the entire cohort. Data supporting peak lactate in lung transplantation as a marker of systemic perfusion adequacy are limited, but elevated lactate level was associated with worse outcomes in a heterogenous off-pump/ECLS support model.[22]

These outcome data provide an initial look at the experience with this circuit in a single-center population and suggest that future studies may be warranted to examine its impact on outcomes in lung transplantation. A final consideration of our outcome results is related to the economics of our circuit. Our hybrid VA-ECMO/CPB circuit costs >90% less than a standalone VA-ECMO circuit. This is important because it provides an economic option for pursuit of an ECMO technique for centers that otherwise may be dissuaded by the cost of a standalone system. Although actual costs are proprietary information of centers, regions, and nations, the dual strength of a variable ECLS approach combined with the lower cost per transplant provide further support for studying our hybrid circuit and its impact on outcomes.

Limitations

It is important that the outcome results of this initial large experience with our novel hybrid circuit be considered in the appropriate context. In this is single-center retrospective descriptive study, there was no control group, and the outcomes data cannot be interpreted as a result of use of the hybrid circuit. Our study occurred over a 5-year period, resulting in variable follow-up, limiting our freedom from death analysis at the 2- and 3-year intervals. Finally, the exclusion of evaluating data from single lung transplantations, ECLS bridge-to-transplantations, and retransplantations may be considered a limitation; however, the growing trend toward primary double lung transplantation as the primary modality of transplantation[23] led our team to choose this cohort to study.

CONCLUSIONS

This report describes our initial experience and outcomes when using a hybrid VA-ECMO/CPB circuit for intraoperative ECLS during lung transplantation. The utility of this circuit lies in the ability of the clinical team to tailor the ECLS of choice, convert from VA-ECMO to CPB with ease, and accomplish this at a significantly reduced cost for our institution compared to a standalone VA-ECMO circuit. Our cohort's significant prevalence of obesity, advanced age, and cardiopulmonary comorbidities of right ventricular dysfunction and elevated PAP suggest that it had more risk factors for increased morbidity and mortality compared to the general lung transplantation population. Implementation of this approach in combination with a structured MDT management protocol may allow for maintenance of VA-ECMO across a wide range of recipient comorbidities, and our experience describes its use without major adverse circuit-related events in a diverse recipient ESLD cohort of 100 patients. This first large report on the circuit experience and outcomes provides foundation for future studies that should focus on the impact of the circuit on intraoperative outcomes, as well as predictors of unplanned conversion to CPB in lung transplantation.

Conflict of Interest Statement

A.K.M. serves as a consultant and scientific advisory board member for Attgeno AB, with all compensation to the Mayo Clinic. T.N. serves on an advisory board for Lung Bioengineering, with all compensation to the Mayo Clinic. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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TABLE E1. Kaplan-Meier estimates of overall survival

Patients, n	Total events	1-y OS rate (95% CI)	2-y OS, % (95% CI)	3-y OS, % (95% CI)
100	15	96.0 (92.2-99.9)	87.3 (80.5-94.7)	81.6 (71.9-92.6)

OS, Overall survival; *CI*, confidence interval.