ECMO support in Lung Transplantation

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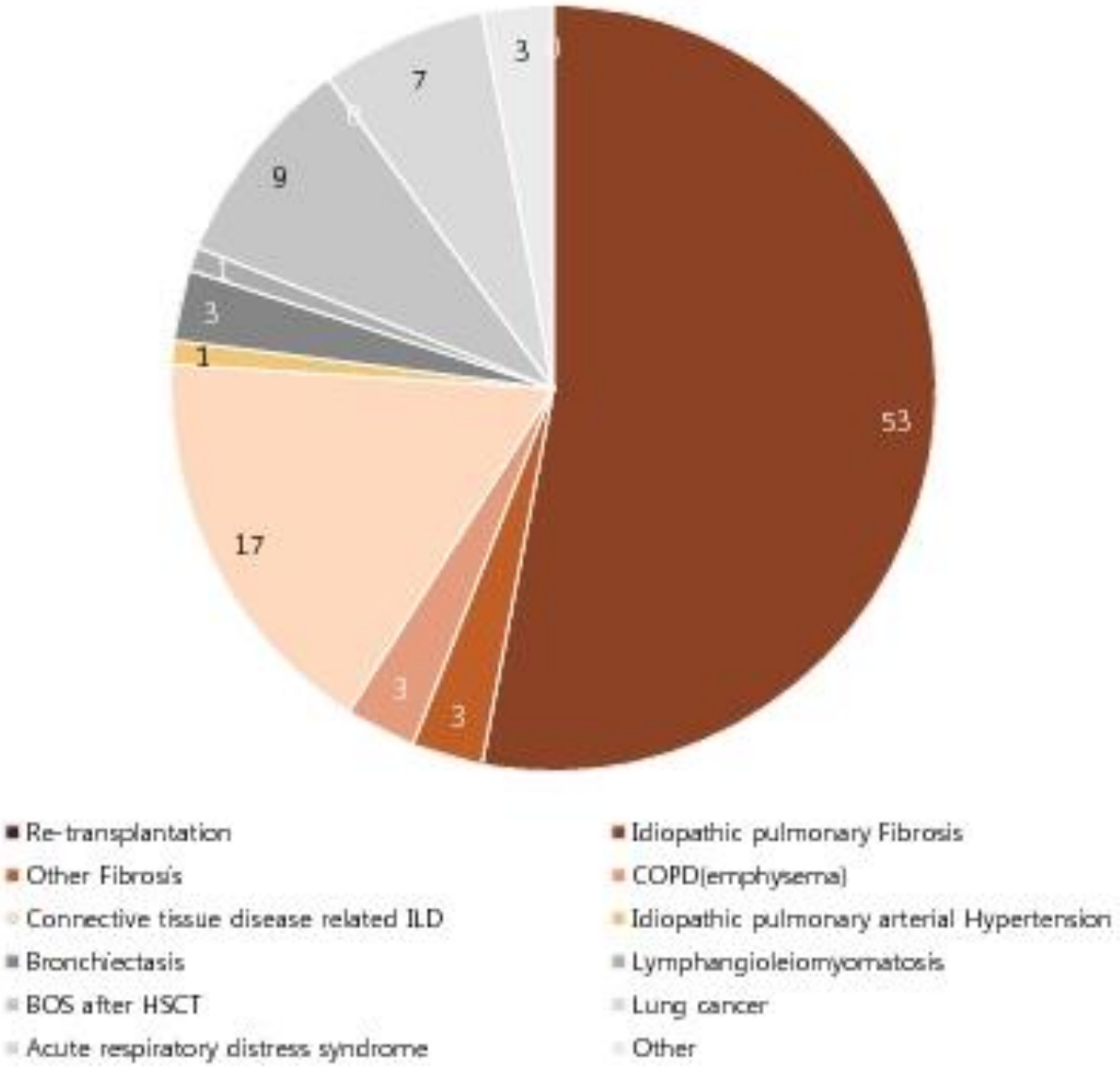
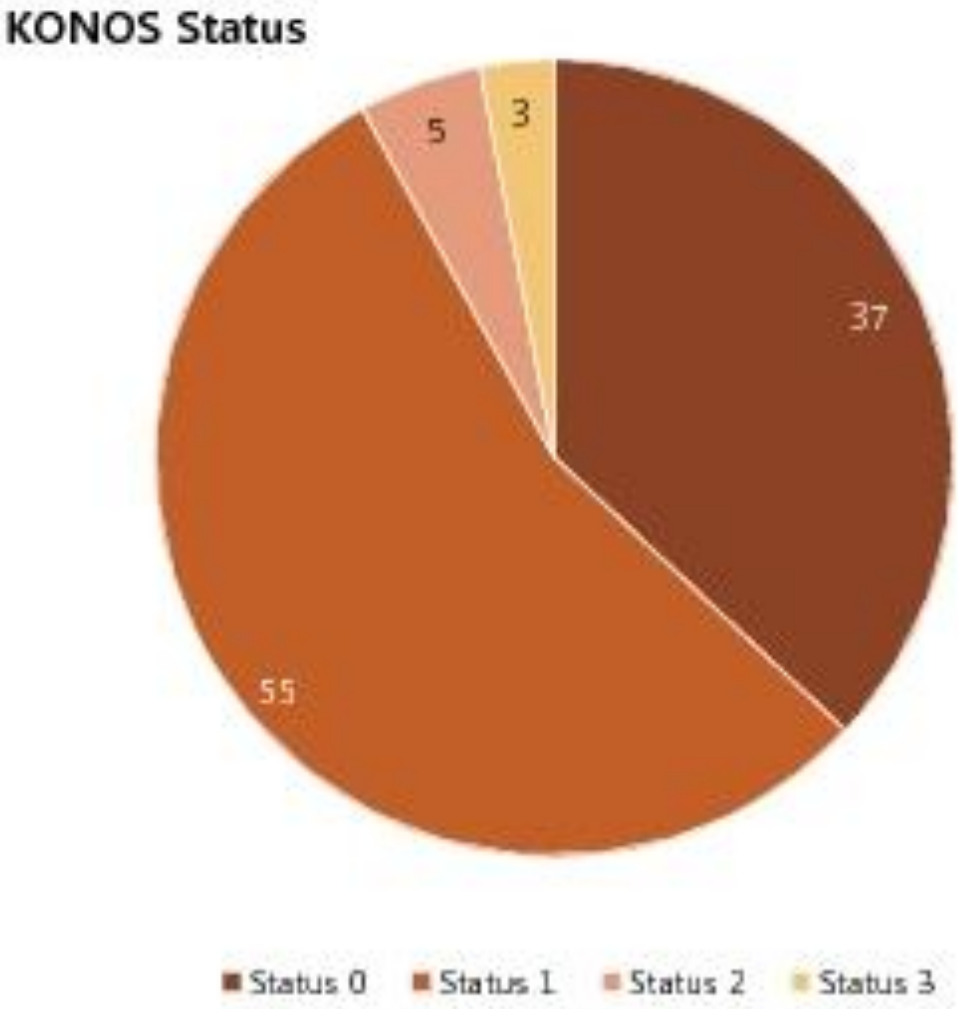
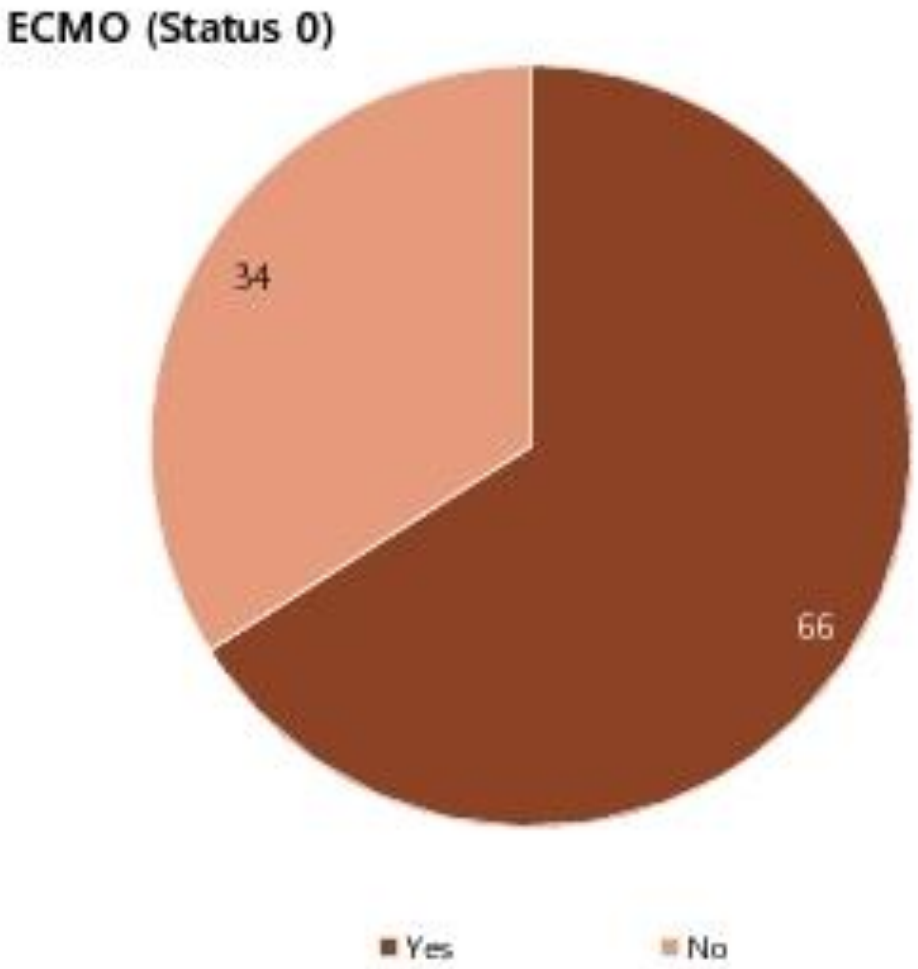
Cause of Lung TPL

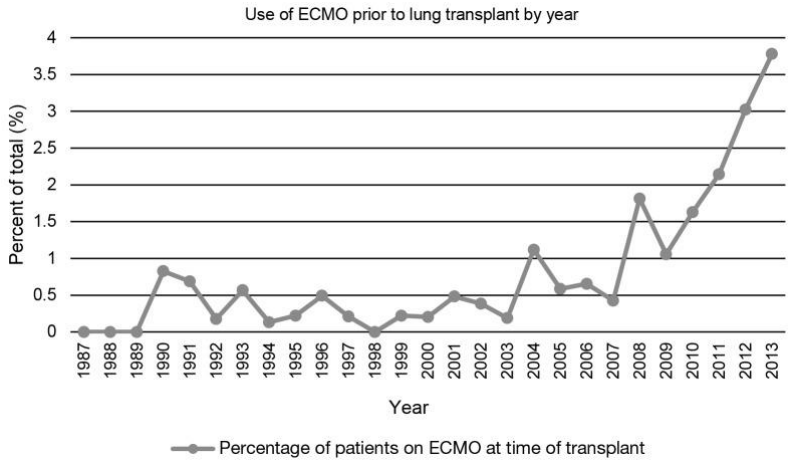




	N
Status 0	41
Status 1	62
Status 2	6
Status 3	3
Total	112

No. of ECMO in Stage 0



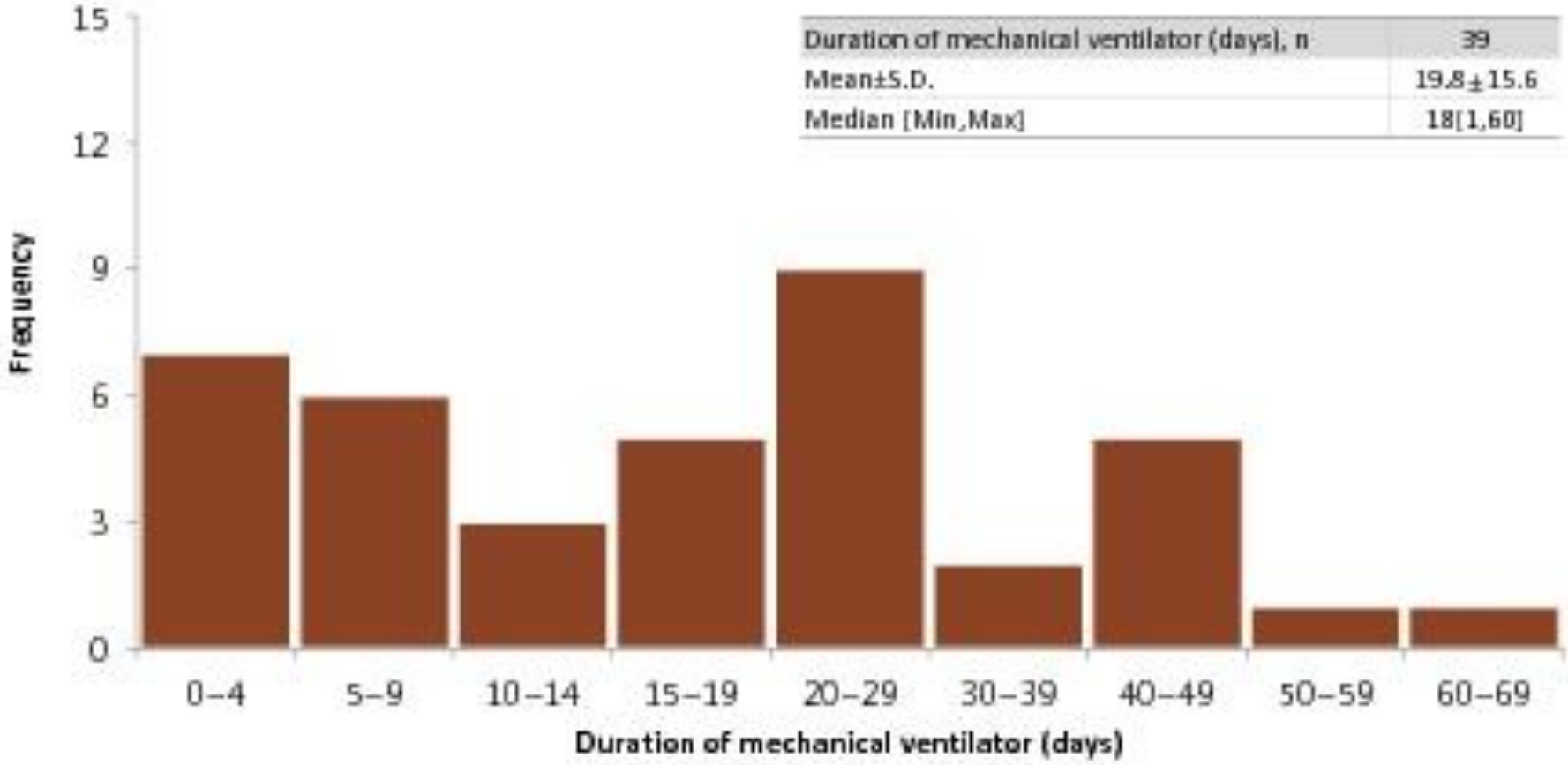


	N
Yes	27
No	14
Total	41

KOTRY annual report LUNG 2017, J Thorac Dis 2014

Duration of MV

Duration of mechanical ventilator (days), n	39
Mean±S.D.	19.8±15.6
Median [Min,Max]	18[1,60]



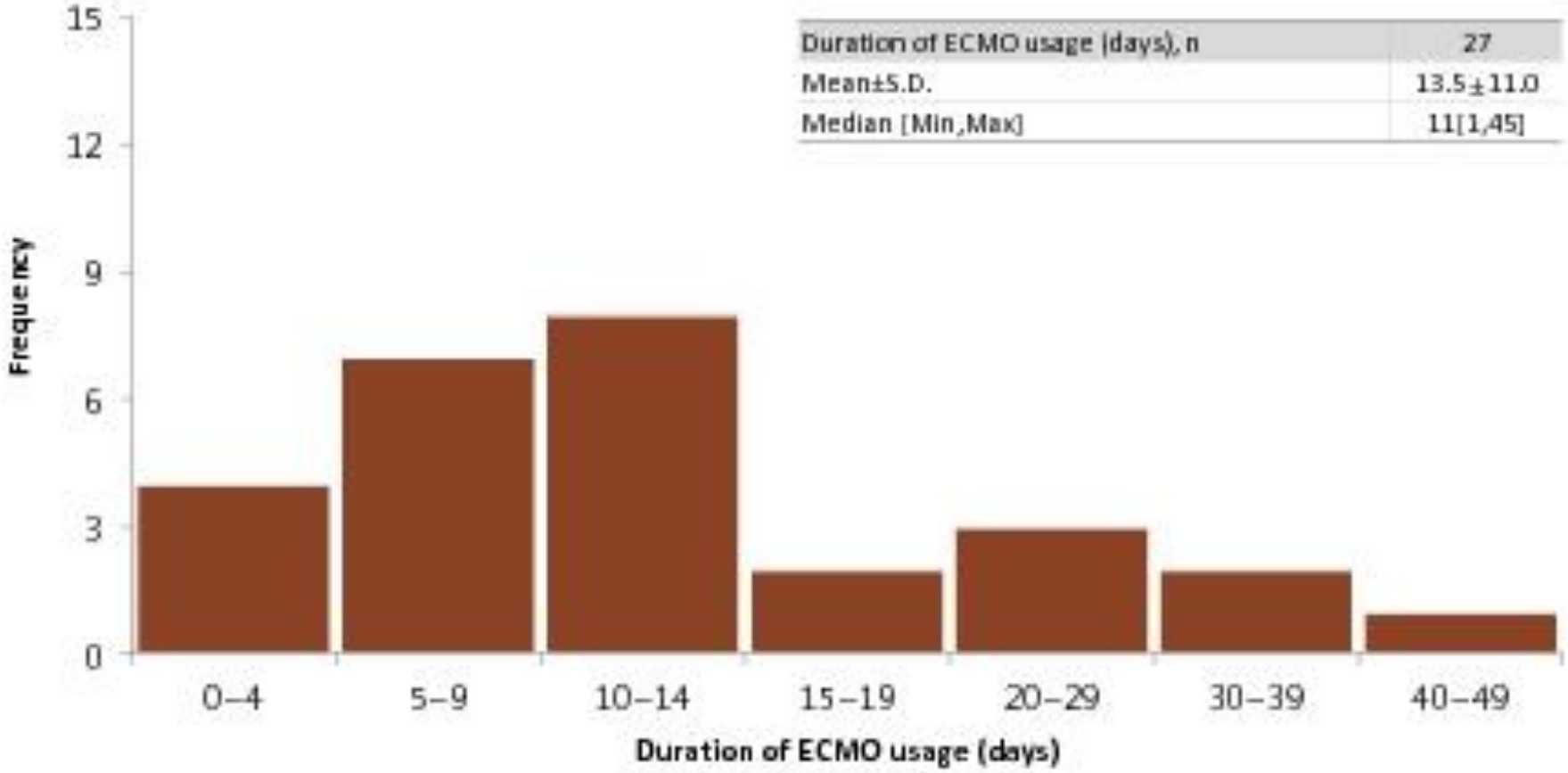
Days	0 ~ 4	5 ~ 9	10 ~ 14	15 ~ 19	20 ~ 29	30 ~ 39	40 ~ 49	50 ~ 59	60 ~ 69
Frequency	7	6	3	5	9	2	5	1	1

Why ECMO in Lung TPL?

- Solutions to deaths on the wait list
- Prevent VILI
- Promote awaken state and mobilization
- Manage right heart failure combined with end-stage lung diseases

Duration of ECMO

Duration of ECMO usage (days), n	27
Mean±S.D.	13.5±11.0
Median [Min,Max]	11[1,45]



Days	0 ~ 4	5 ~ 9	10 ~ 14	15 ~ 19	20 ~ 29	30 ~ 39	40 ~ 49
Frequency	4	7	8	2	3	2	1

ECMO in Lung transplantation (TPL)

- Before
  - Rescue for AE of underlying diseases
  - Long-term mechanical support for prevent VILI
  - Awake, and Facilitate rehabilitation in ICU
- During
  - Intraoperative circulatory/respiratory support instead of CPB
- After
  - Rescue for Primary Graft Dysfunction

Appropriate patient selection

Appropriate patient selection

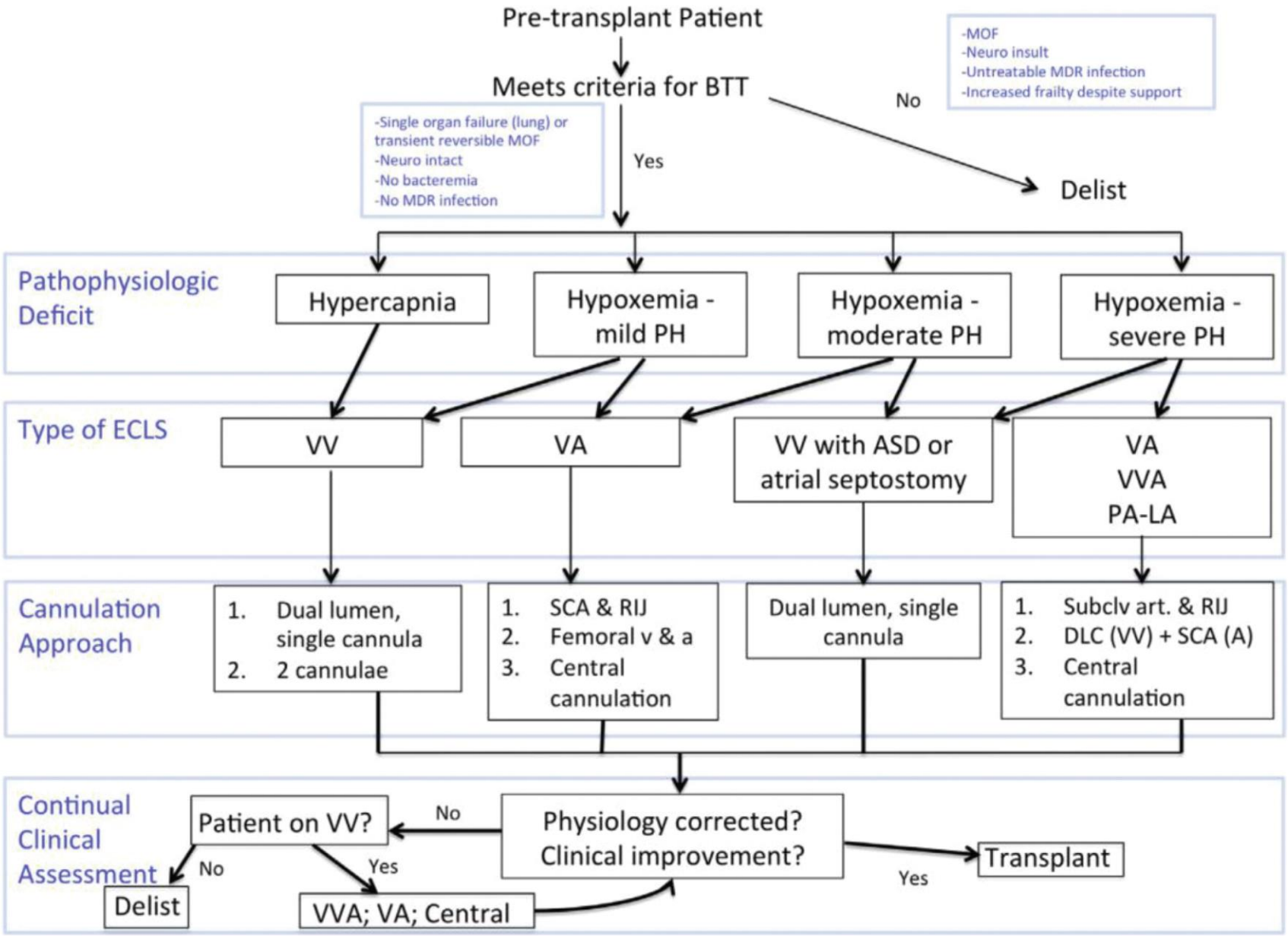
- NO RCTs
- Not too early, nor too late
  - Physical deconditioning is considered by many transplantation centers to be a strong relative contraindication to lung TPL
  - Prior to the onset of cardiac arrest and irreversible extrapulmonary end-organ function
- ECMO itself may introduce the risk for important pretransplant complications
  - Hemorrhage -> transfusion -> allograft availability
  - ICU acquired complications: ECMO-related issues??

ECMO before Lung TPL

- Minimization of Sedation and Awake ECMO
- As possible as extubation or early tracheostomy
- Early mobilization
  - Interdisciplinary approach without any doubt
- Restrictive transfusion strategy
  - Lowering anticoagulation during ECMO is POSSIBLE under maintaining sufficient blood flow
  - Still remained issues

Consideration of ECMO configuration

Physiologic Abnormalities	ECMO Configuration
Hypercapnia without hypoxemia	Venovenous Arteriovenous Femoral artery to femoral vein
Hypoxemia with no pulmonary hypertension	Venovenous
Hypoxemia with mild pulmonary hypertension	Venovenous, consider venoarterial
Hypoxemia with moderate to severe pulmonary hypertension	Venoarterial Internal jugular vein to subclavian artery Femoral vein to femoral artery (+/- internal jugular venous return, i.e. venoarterial venous) Venovenous via dual-lumen cannula with atrial septal defect or atrial septostomy Arteriovenous Pulmonary artery to left atrium



Thorac Surg Clin, 2015

Different configuration

	2-site VV	VV via DLC	VV via DLC with ASD	Femoral VA	Upper-body VA	Hybrid configurations (VVA or VAV)	PA-LA
Upper-body oxygen delivery	+++	+++	+++	-/+	+++	++	+++
RV unloading*	-	-	++/+++	+++	+++	++	+++
Effect on LV afterload	-	-	-	+++	++	++/+++	-
Mobilization potential	+	+++	+++	-/+	+++	-/+	+++
Cannulation difficulty	+	++	++	+	+++	++	+++

DLC=dual-lumen cannula; ASD=atrial septal defect; mPAP=mean pulmonary arterial pressure; PA-LA=pulmonary artery to left atrium; RV=right ventricle; LV=left ventricle; VV=venovenous; VA=venoarterial; VAV=venoarterial venous; VVA=venovenous arterial

(-)=negligible; (+)=low; (++)=moderate; (+++)=high

*Based on chronic RV loading conditions. The effect of relieving any component of RV loading due to acute hypoxemia or hypercapnia will be variable.

Adapted from Biscotti M, Sonett J, Bacchetta M. ECMO as bridge to lung transplant. Thoracic surgery clinics 2015; 25:17-25, Table 1.

ECMO Bridging to Lung TPL
SNUBH Experiences

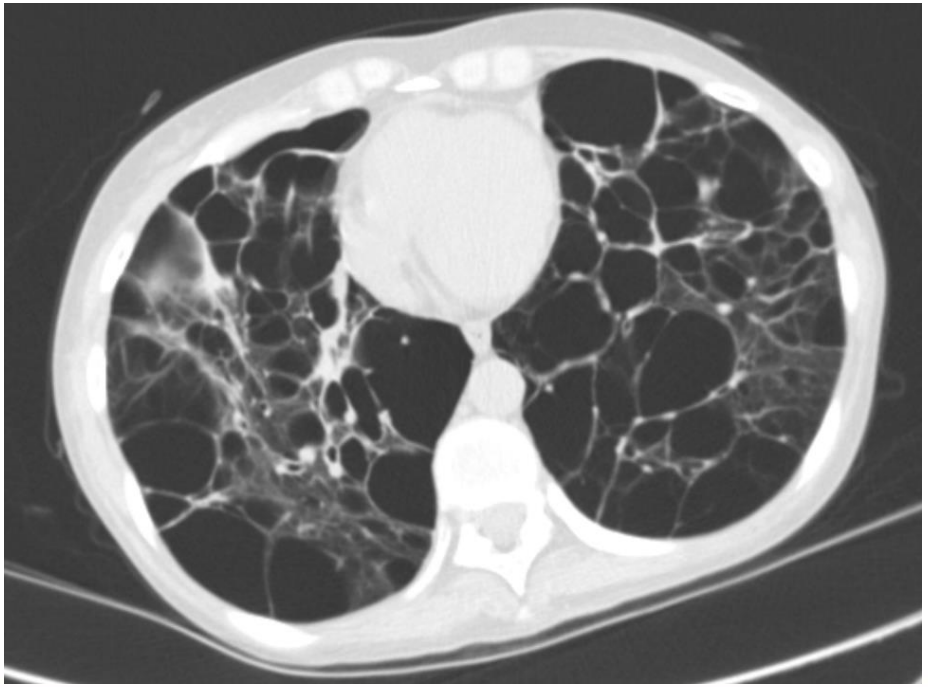
F/36 ECMO #43

M/36 ECMO #35

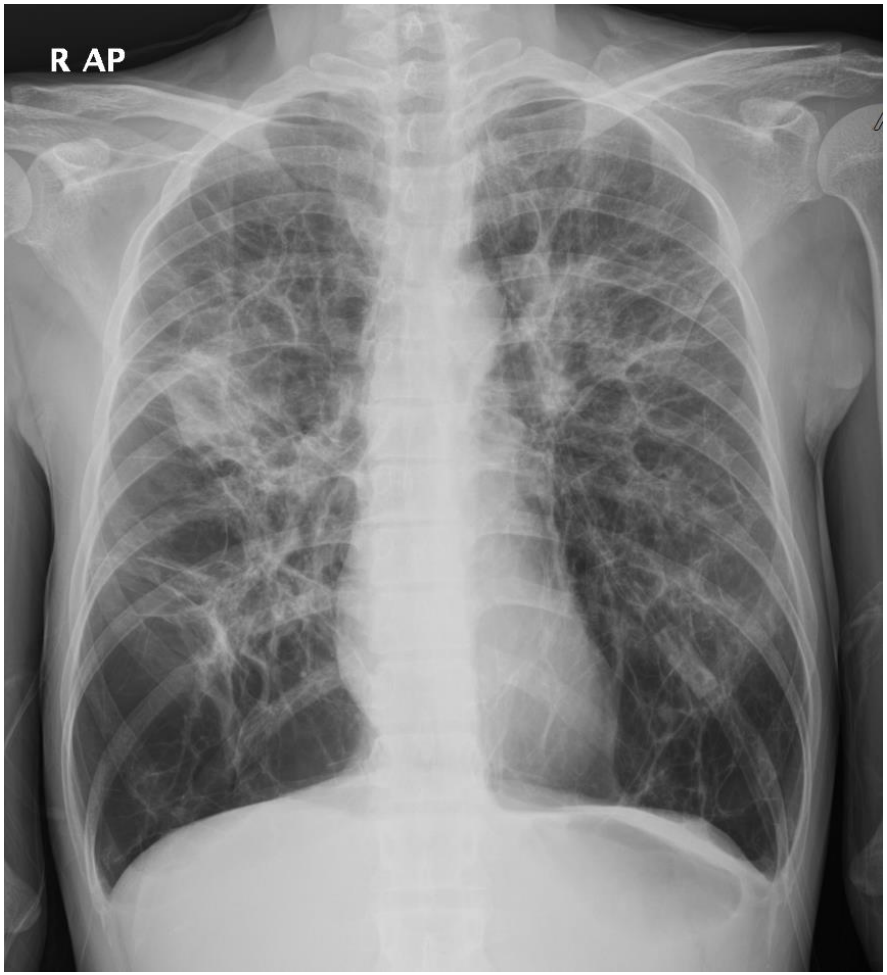
M/53 ECMO #47

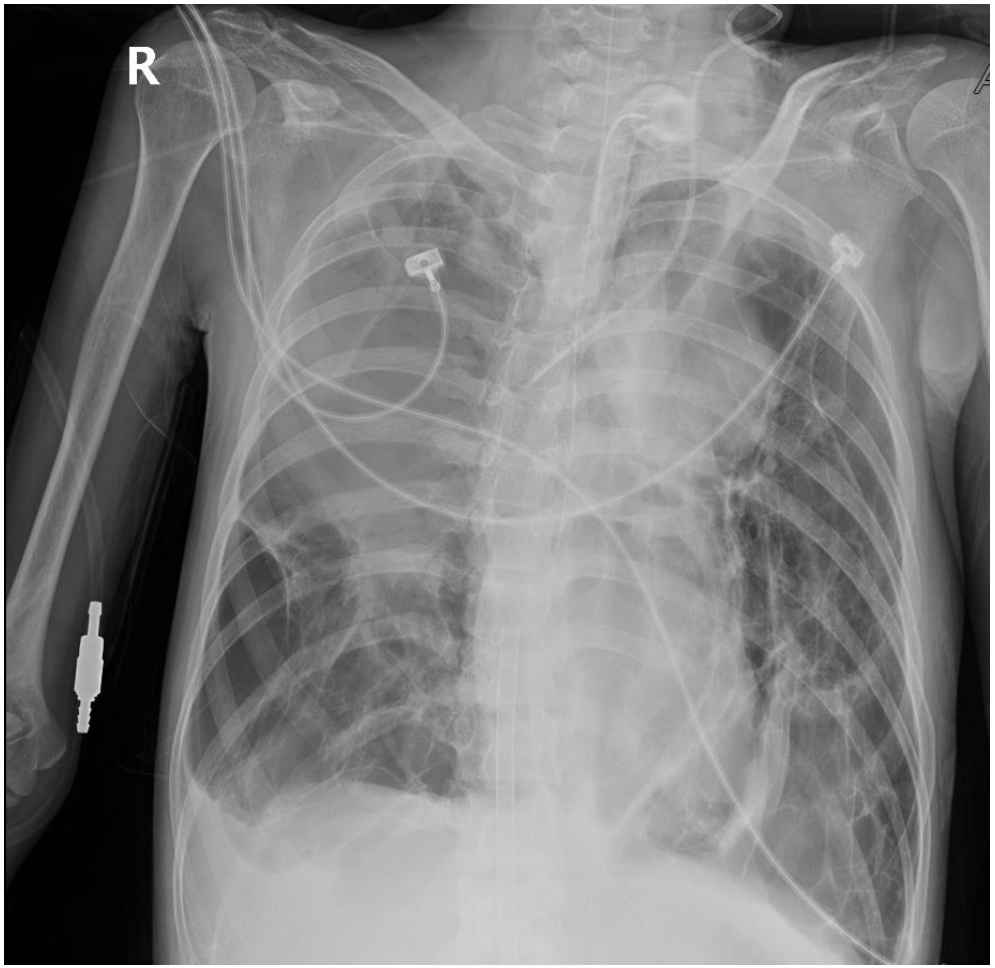
F/36

- Sjogren syndrome ILD
  - Type 2 respiratory failure
  - Various opportunistic infections
  - Frequent TPL listed and delisted



Hospital course





Hospital course

2018-06-08 MICU admission
HFS 0.9/60L, saturation 83-86% + drowsy
pH 7.195 pCO2 117.6 SaO2 85.4

Intubation + bridging VV ECMO insertion
Oral bleeding, E-tube fresh blood : STOP heparinization

2018-06-22 ECMO oxygenator change(elective) & PDT
2018-06-28 SIMV mode ventilator OFF & "Awakening"

2018-07-13 Successful lung TPL
(T-cannula removal at OR)

2018-07-14 Post-op bronchoscopy (RLL inflamation, intact anastomosis sites)
Extubation → Post-extubation respiratory distress (4hours)
Bronchoscopic guided T-cannula re-insertion & ventilator apply

"Awake" ECMO

- Avoidance of complications associated with chronic immobility and sedation
- Active physiotherapy which includes breathing and limb exercises
  - prevent pressure sores, muscle loss, joint stiffness, softening of bones
- Meet family and friends use phone and computers, view television
  - Keep patients mood elated
- Eat and drink normally
- Suboptimal therapy or complications can be detected at earlier stage

CHEST Original Research
TRANSPLANTATION

Organ Allocation Waiting Time During Extracorporeal Bridge to Lung Transplant Affects Outcomes

Stefania Crotti, MD; Giorgio A. Iotti, MD; Alfredo Lissoni, MD; Mirko Belliato, MD; Marinella Zanierato, MD; Monica Chierichetti, MD; Guendalina Di Meo, MD; Federica Meloni, PhD; Marilena Pappalettera, MD; Mario Nosotti, MD; Luigi Santambrogio, MD; Mario Viganò, MD; Antonio Braschi, MD; and Luciano Gattinoni, MD

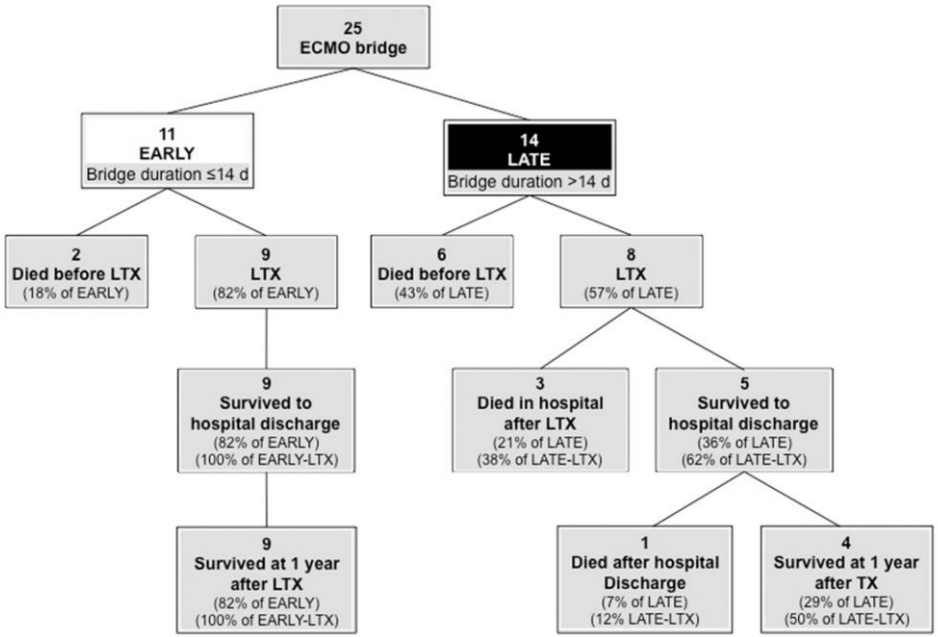


FIGURE 2. Outcomes of the Early group compared with the Late group. See Figure 1 legend for expansion of abbreviations.

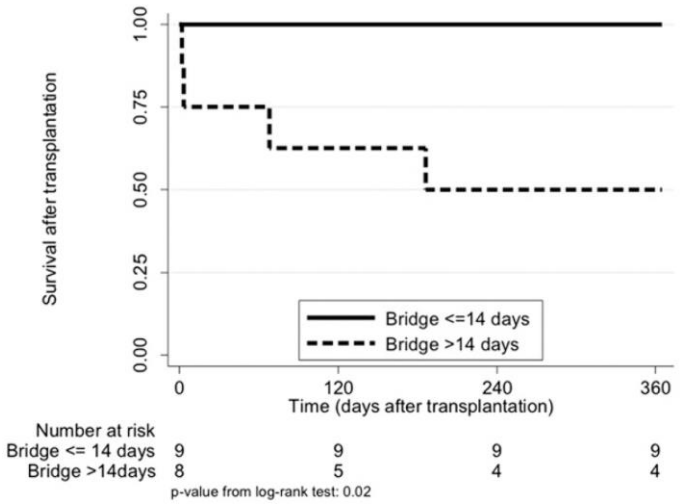


FIGURE 3. Population survival after lung transplant: Kaplan-Meier survival curves in Early and Late groups.

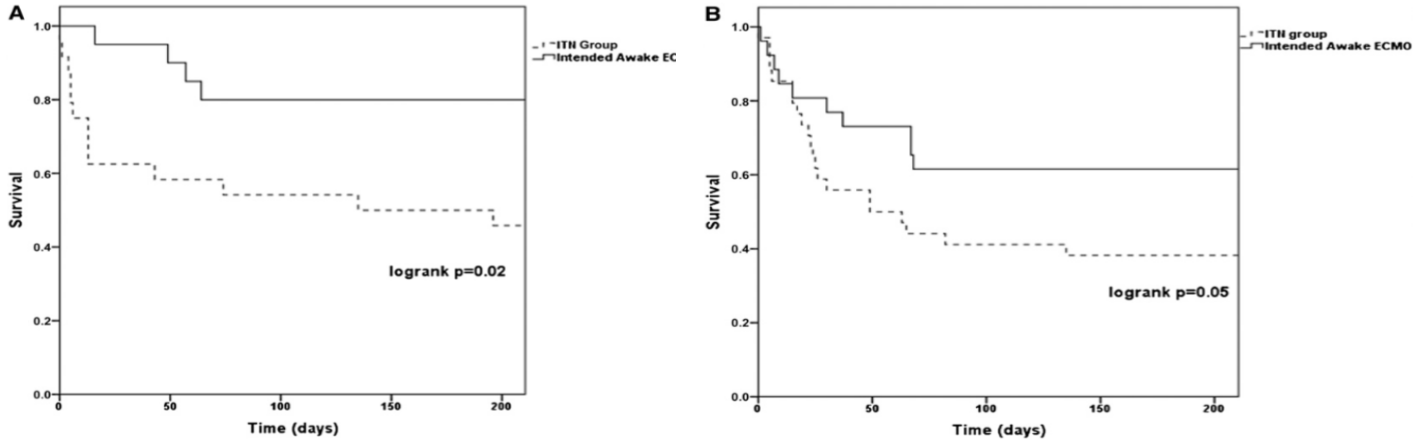
Extracorporeal Membrane Oxygenation in Awake Patients as Bridge to Lung Transplantation

Thomas Fuehner[1], Christian Kuehn[2], Johannes Hadem[3], Olaf Wiesner[1], Jens Gottlieb[1], Igor Tudorache[2], Karen M. Olsson[1], Mark Greer[1], Wiebke Sommer[2], Tobias Welte[1], Axel Haverich[2], Marius M. Hoeper[1], and Gregor Warnecke[2]

[1]Department of Respiratory Medicine, [2]Department of Cardiothoracic, Transplant and Vascular Surgery, and [3]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

TABLE 1. COMPARISON OF PATIENT CHARACTERISTICS AND OUTCOMES IN THE AWAKE ECMO GROUP AND THE MECHANICAL VENTILATION GROUP

	Mechanical Ventilation Group	Awake ECMO Group	*P* Value
Bridging to Tx			
Bridging time, median, range	15 (1–71)	9 (1–45)	0.25
Death before Tx, n (%)	10 (29)	6 (23)	0.58
Post-transplant period			
Transplantation, n (%)	24 (71)	20 (77)	
DLTx, n (% of transplant patients)	21 (84)	20 (100)	0.06
Death after LuTx, n (% of transplant patients)	12 (50)	4 (20)	0.02
Days on MV after LuTx (survivors only), median (range)	37 (1–72)	14 (0–64)	0.04
Extubation within 24 h after LuTx, n (%)	1 (4)	5 (25)	0.10
Renal failure requiring hemodialysis after Tx (survivors only), n (%)	2 (6)	1 (4)	0.66
Days on ICU (survivors only), median (range)	39 (4–74)	18 (1–69)	0.07
Days in hospital stay (survivors only), median (range)	67 (23–90)	38 (20–87)	0.06



Awake Extracorporeal Membrane Oxygenation as Bridge to Lung Transplantation: A 9-Year Experience

Mauer Biscotti, MD, Whitney D. Gannon, MSN, Cara Agerstrand, MD, Darryl Abrams, MD, Joshua Sonett, MD, Daniel Brodie, MD,* and Matthew Bacchetta, MD*

Division of Cardiothoracic Surgery, Department of Surgery, and Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University Medical Center, New York, New York

- large, single-center experience
- Patients who received ECMO as a bridge to lung transplantation from January 1, 2007 through July 10, 2016. (N = 72)
- 40/72 (55.6%) underwent TPL procedure, 37/40 (92.5%) survived to discharge, 21/25 (84.0%) survived for 2 years

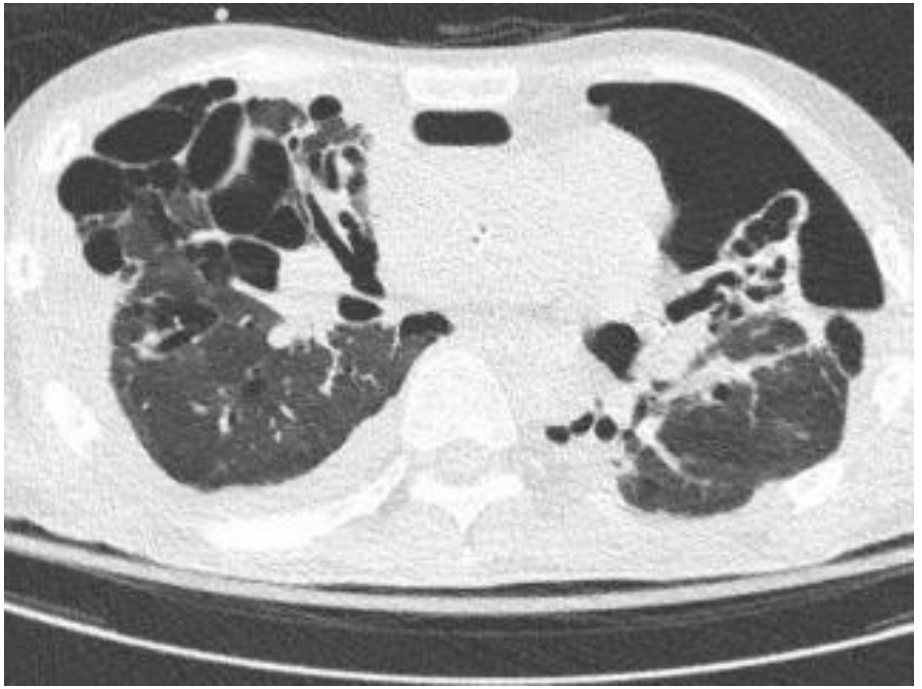
Characteristics	Lung Transplantation Performed (n = 40) Mean/Median or No. (%)	Lung Transplantation Not Performed (n = 32) Mean/Median or No. (%)	*p* Value
MV to ECMO	0 (0–2)	0 (0–2)	0.784
Hospitalization to transplantation/death/delist	25 (13–40)	30 (14–49.75)	0.626
ICU to transplantation/death/delist	19 (11.25–34.25)	20 (12.25–35.25)	0.932
Pre-ECMO pH	7.28 ± 0.14	7.22 ± 0.19	0.200
Pre-ECMO PCO_2 (mm Hg)	82.8 ± 42.6	84.8 ± 40.9	0.838
Pre-ECMO PO_2 (mm Hg)	136.4 ± 99.2	107.2 ± 96.6	0.223
Inotropy/vasopressor	28 (70%)	30 (93.8%)	0.011
Pre-ECMO pulmonary artery pressure (mm Hg)	76.1 ± 16.5	73.8 ± 18.7	0.775
ECMO characteristics			
Cannulation type			0.549
Venovenous	25 (62.5%)	20 (62.5%)	
Venoarterial	14 (35%)	9 (28.1%)	
Venovenoarterial	1 (2.5%)	2 (6.2%)	
Pulmonary artery to left atrium	0 (0)	1 (3.1%)	
Time between (days [IQR])			
ECMO to transplantation/death/delist	12 (6.25–18.75)	12 (7.5–23)	0.475
ECMO flow/calculated cardiac output	76.1% ± 16.5%	73.8% ± 18.7%	0.581
ECMO configuration change	7 (17.5%)	11 (34.4%)	0.100
Tracheostomy	15 (37.5%)	19 (59.4%)	0.065
Ambulation	32 (80%)	18 (56.2%)	0.030

M/36

#1. AML, AML1/ETO+, FLT3(+ITD)

s/p CyTBI conditioning with alloPBSCT (2014.2.11)

#2. Lung GVHD (2015.8)



Hospital course

2018-06-07 Admission

Type II respiratory failure (pCO2~130)

2018-06-14 ECCO2R #1 (pCO2 130 → 80) – RF side

2018-06-18 Abdomen CT : appendicitis

2018-07-03 ECCO2R membrane change #2

2018-06-28 Abdomen CT :

perforated appendicitis, abscess

2018-07-04 Open Ileocecectomy (spinal anesthesia)

- hematochezia, post-op ileus

2018-07-13 CFS for bleeding control

2018-07-17 NJ tube insertion (post-op ileus)

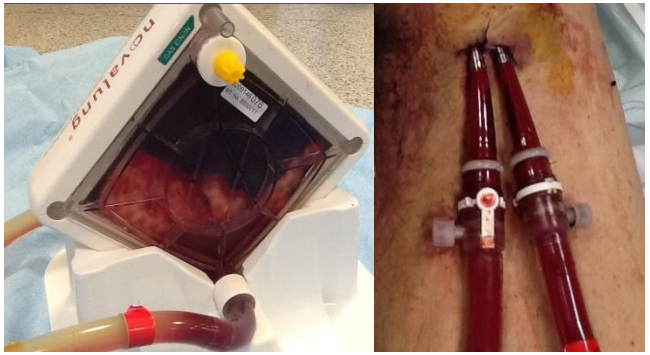
2018-07-18 ECCO2R, RF → LF

2018-07-26 Pseudoaneurysm repair, Rt ECCO2R site

2018-07-27 VV-ECMO (RF to RJ)

2018-08-16 ECMO oxygenator change

2018-08-23 Lung TPL done, Finally



Dark sides of ECMO

Table 2. Side effect and potential complication during ECMO

Surgical site complication including bleeding
Renal dysfunction
Dysarrhythmia
Limb ischemia and amputation of cannulated limbs
Hemorrhage associated with anticoagulation requirements
Circuit-associated inflammation or coagulopathy
Hemolysis
Mechanical events (eg, failure of the oxygenator, thrombosis)
Infection
Neurological complications

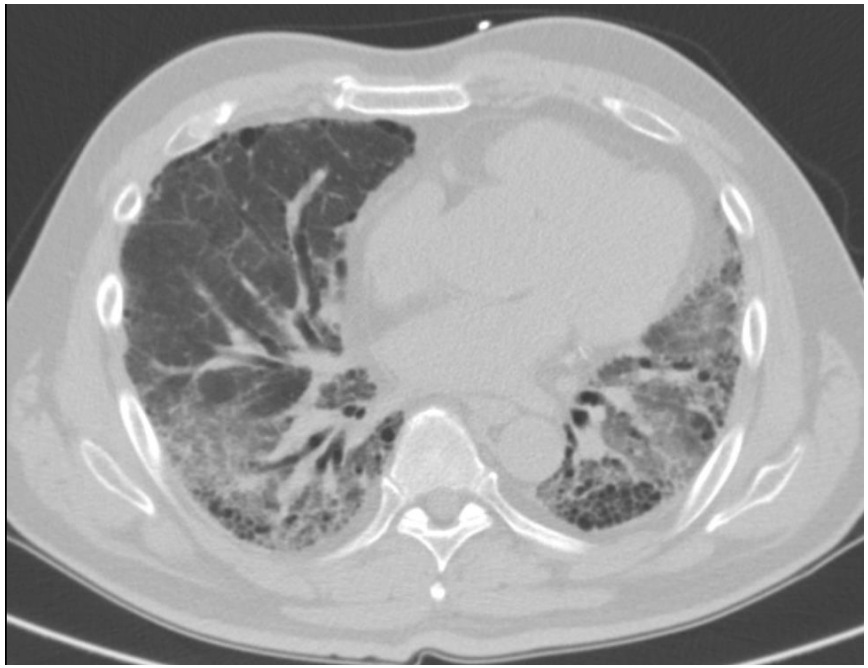
ECMO, extracorporeal membrane oxygenation.

M/53

#1. Fibrotic NSIP

#2. Alleged severe pulmonary HTN

#3. Type I respiratory failure



Hospital course

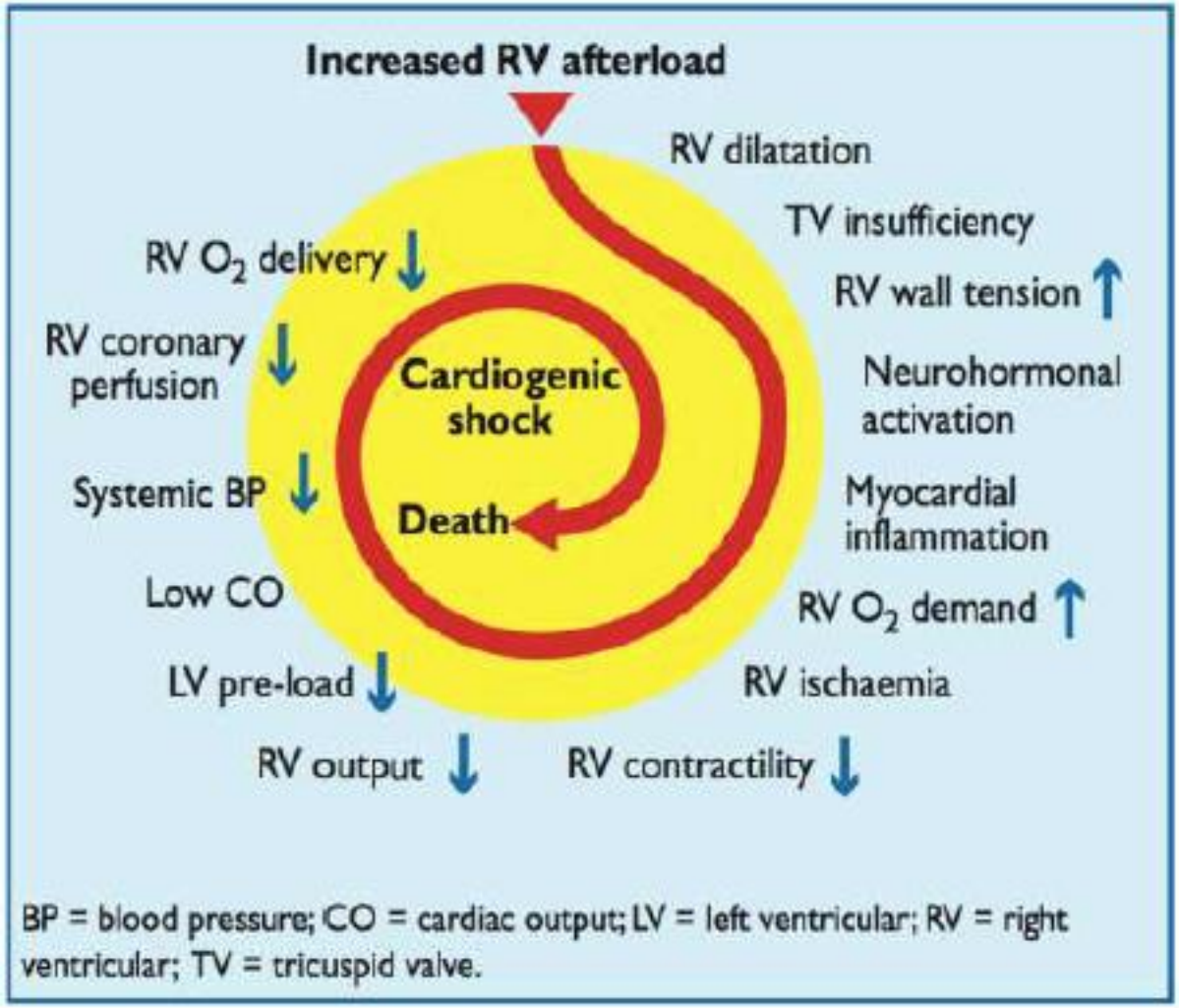
2018-10-20 Type I respiratory failure, Intubation
VV-ECMO insertion
2018-10-24 Early tracheostomy
2018-10-29 Oxygenator membrane change #1
Left femoral ECMO insertion site repair

2018-11-03 Anti heparin Ab (+), Hepain induced thrombocytopenia
→ Argatroban

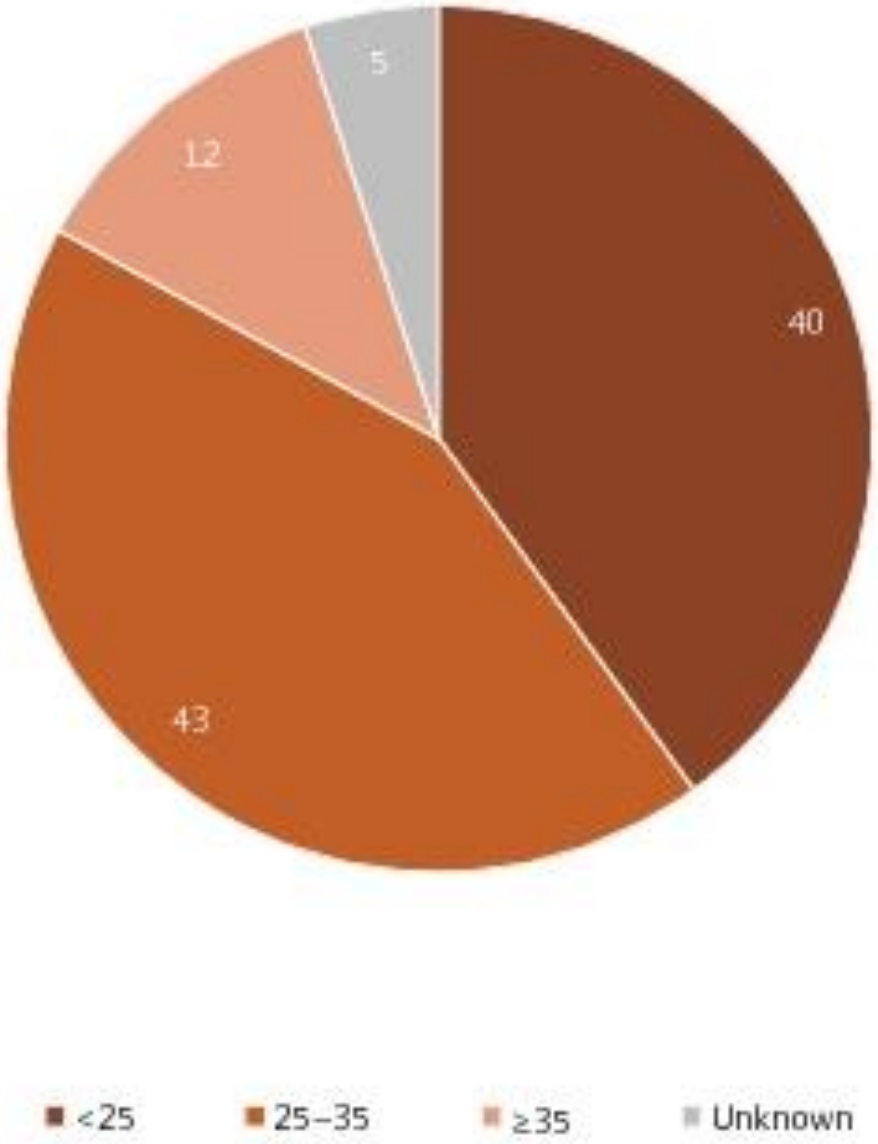
2018-11-14 Oxygenator membrane change #2
2018-11-15 D-shaped LV, severe PH
→ Milrinone infusion combined with iNO
OxyRVAD consider
2018-11-17~26 Anti heparin Ab (–) X2
→ Heparin restart

2018-12-05 Successful Lung TPL

RV failure (Cor pulmonale)

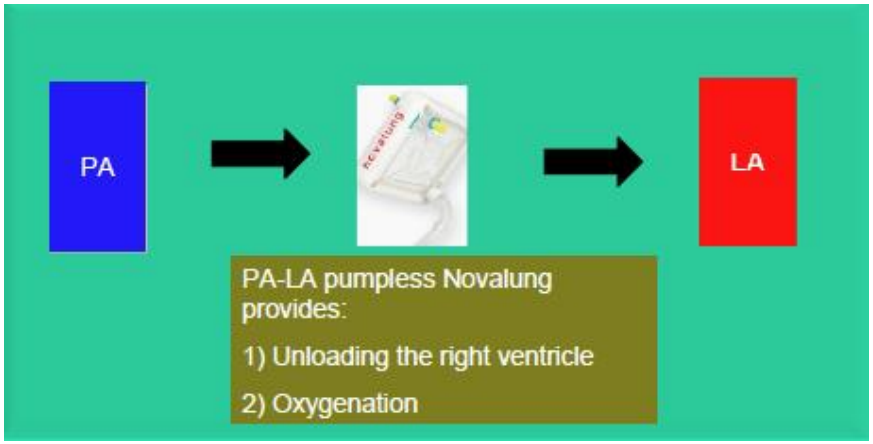


PAH at Pre-TPL



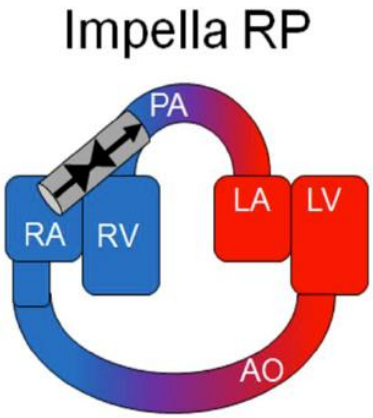
Two approaches using ECMO (not VA) -Bridge to recovery or transplant-

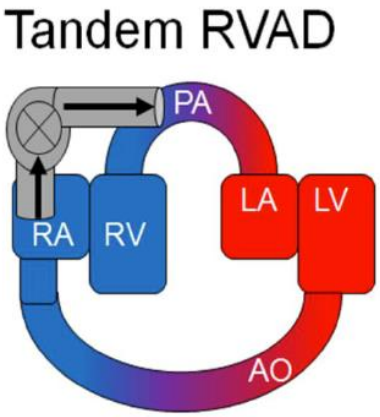
- PA to LA (Lt Atrium)



  - No pump
  - Direct thromboemboli to systemic circulation

- RA (Rt Atrium) to PA



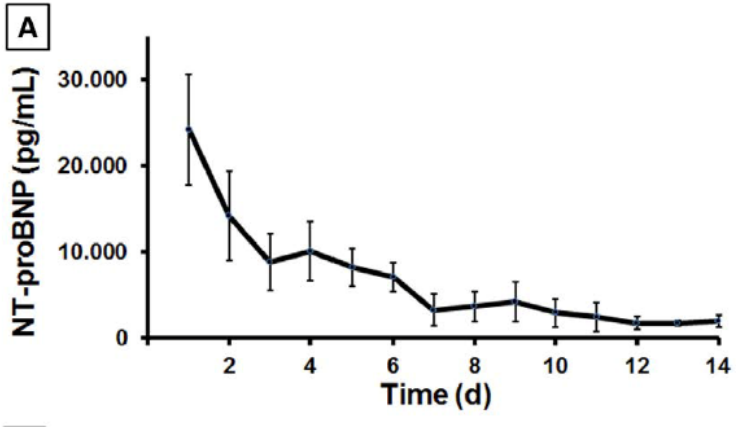


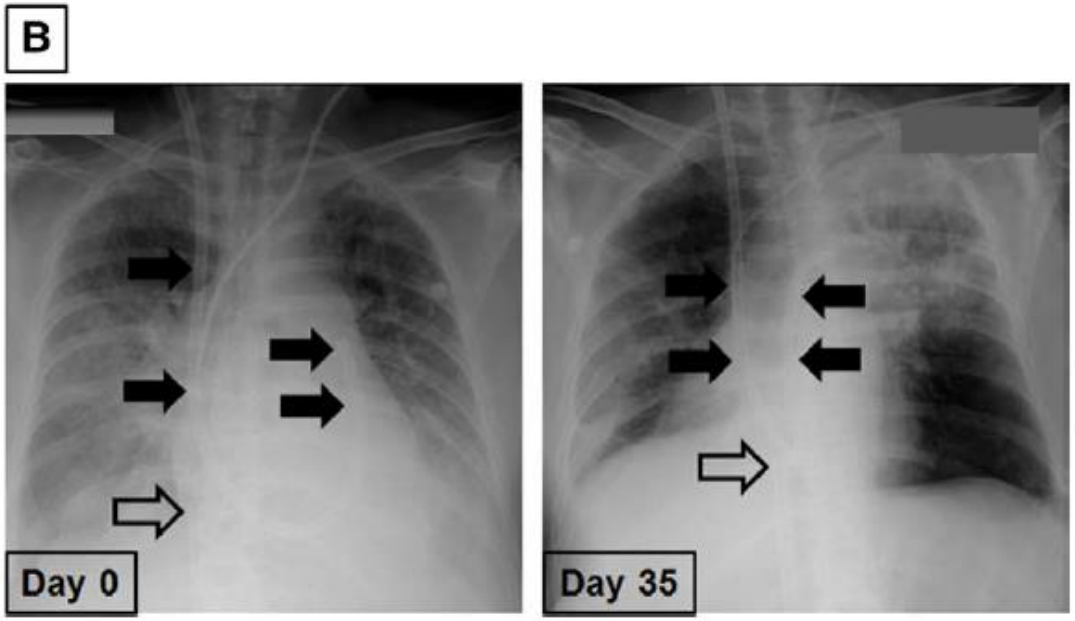
  - Yes pump
  - Thromboemboli to pulmonary circulation

ASAIO Journal 2018

Brief Communication

Percutaneous Mechanical Circulation Support Combined with Extracorporeal Membrane Oxygenation (oxyRVAD) in Secondary Right Heart Failure





ECMO during Lung TPL

- Intraoperative support, Replacement CPB
  - Stabilize hemodynamic variables
    → Prevent "first-lung syndrome"
  - Enhance protective ventilation and avoid 100% oxygen
    → Prevent "reperfusion injury"

- CPB vs. ECMO
  - CPB: Marked systemic inflammatory response, High anticoagulation needs, Increased risk of PGD
  - ECMO: Lower post-TPL MV requirements, ICU and hospital LOS, Rates of hemorrhage, and Need for reoperation
  - Overall survival did NOT different between CPB and ECMO currently

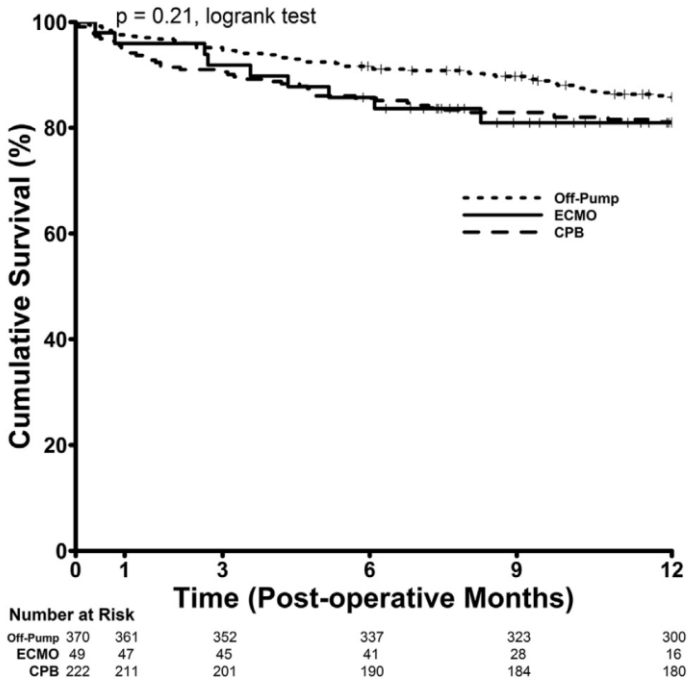
Intraop ECMO(VA) vs. CPB

Table 2. Operative Data

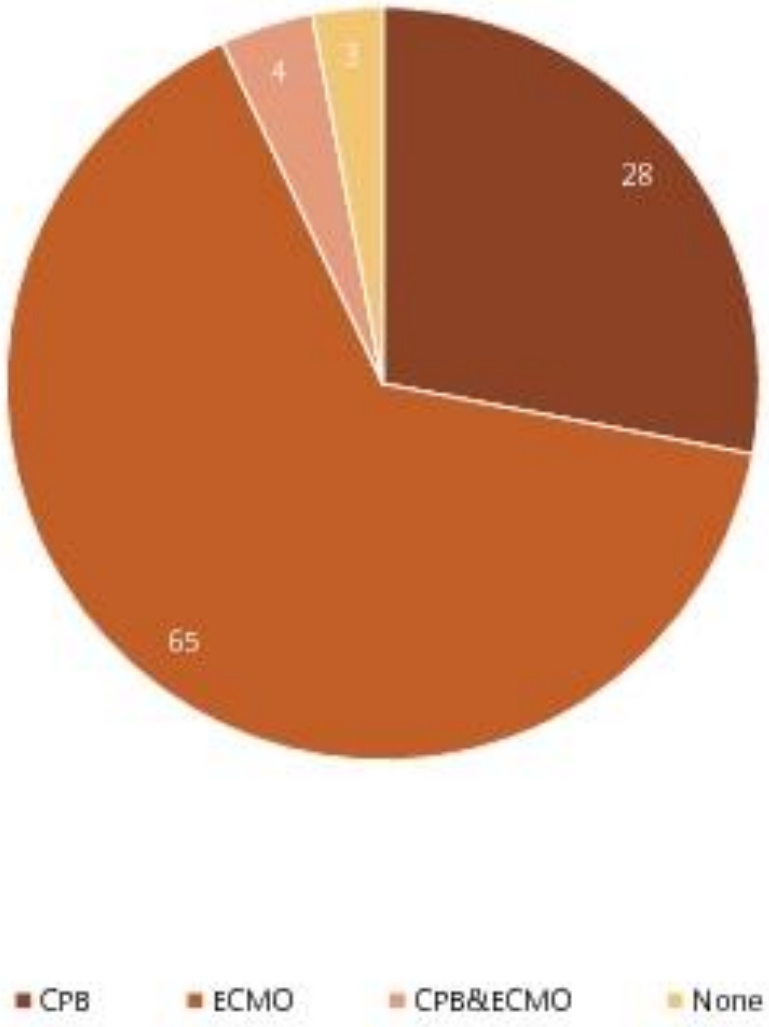
Characteristic	CPB (n = 222)	ECMO (n = 49)	*p* Value (CPB vs ECMO)
Approach, n (%)			0.21
Anteroaxillary/ Anterolateral	163 (73.5%)	42 (85.7%)	
Clamshell	55 (24.8%)	7 (14.3%)	
Median sternotomy	4 (1.8)	0 (0.0%)	
Transplant type, n (%)			0.36
Double	214 (96.4%)	49 (100%)	
Single	8 (3.6%)	0	
Lobar transplant, n (%)	19 (8.6%)	12 (24.5%)	<0.01
Associated cardiac procedures, n (%)	54 (24.5%)	0 (0.0%)	<0.01
CABG	6		
AVR	2		
TV repair	10		
PFO/ASD repair	34		
Other	2		
Ischemic time (minutes, mean ± SD)	363.2 ± 75.5	375.2 ± 66.1	0.29
Time of support, minutes			<0.01
Mean ± SD	232.5 ± 88.6	366.6 ± 144.0	
Median (range)	242 (15–576)	327 (113–717)	

Table 5. Complications

Variable	CPB (n = 222)	ECMO (n = 49)	*p* Value (CPB vs ECMO)
Major intraoperative complications n (%)	1 (0.5%)[a]	1 (2%)[b]	
Reoperation For bleeding n (%)	39 (17%)	4 (8.2%)	0.13
Postoperative complications n (%)			
Renal failure requiring dialysis	49 (22.1%)	4 (8.2%)	0.03
Postoperative ECMO[d] (severe PGD)	34 (15.3%)	9 (18.3%)	0.83
Stroke/CVA	7 (3.2%)	1 (2.0%)	1.00
Atrial fibrillation	69 (31.1%)	16 (32.7%)	1.00
Mortality n (%)			
30 days	11 (5.0%)	2 (4.1%)	1.00
6 months	32 (14.4%)	7 (14.3%)	1.00
1 year	42 (18.9%)	9 (19.1%)	–



Intraoperative support device



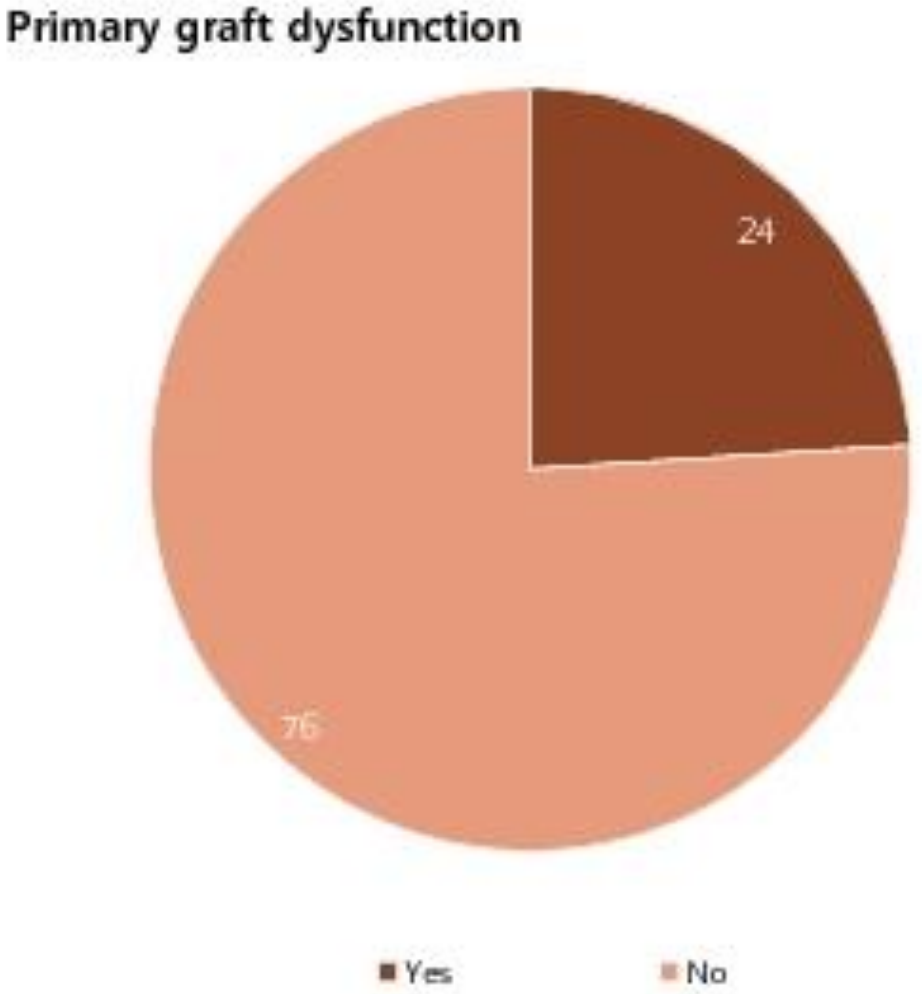
	N
CPB	31
ECMO	73
CPB&ECMO	5
None	3
Total	112

ECMO after Lung TPL

- Normally, we need “NO MORE” ECMO after lung TPL

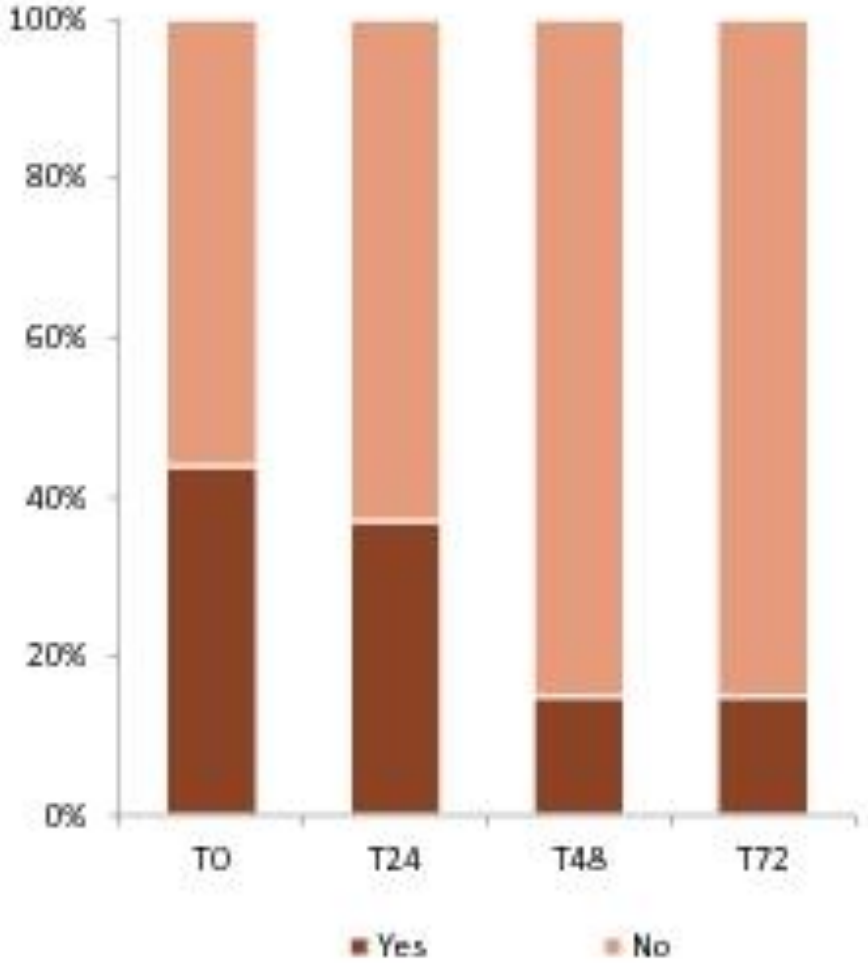
- Post-transplant rescue
  - Management of Primary graft dysfunction (traditionally)
  - Bridge to re-transplantation

Primary Graft Dysfunction



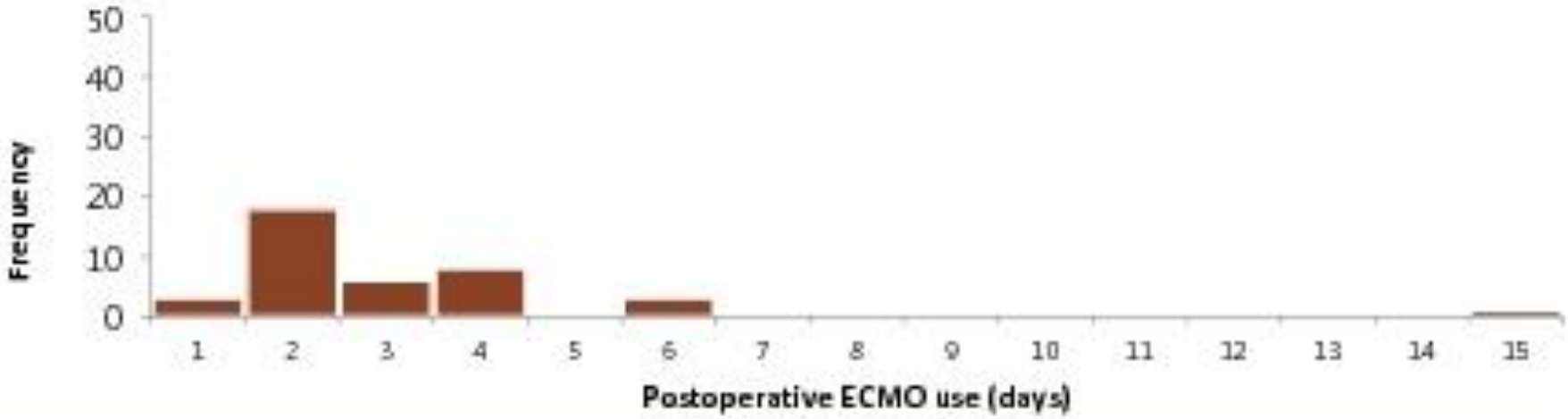
	Total
Yes	27
No	85
Total	112

ECMO



ECMO	T0	T24	T48	T72
Yes	12	10	4	4
No	15	17	23	23
Total	27	27	27	27

Postop ECMO use



Postoperative ECMO use (days)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Frequency	3	18	6	8	0	3	0	0	0	0	0	0	0	0	1

Limitations to Bridge to Lung TPL

- Lack of a destination device such as implantable VAD
- Can't receive lungs finally …
  - Shortage of donor organs
  - Compromising patient's candidacy while awaiting TPL
- Happens the "bridge to nowhere"
  - Ethical dilemmas
  - Give an insight prior to initiation of ECMO
  - Palliative end-of-life care

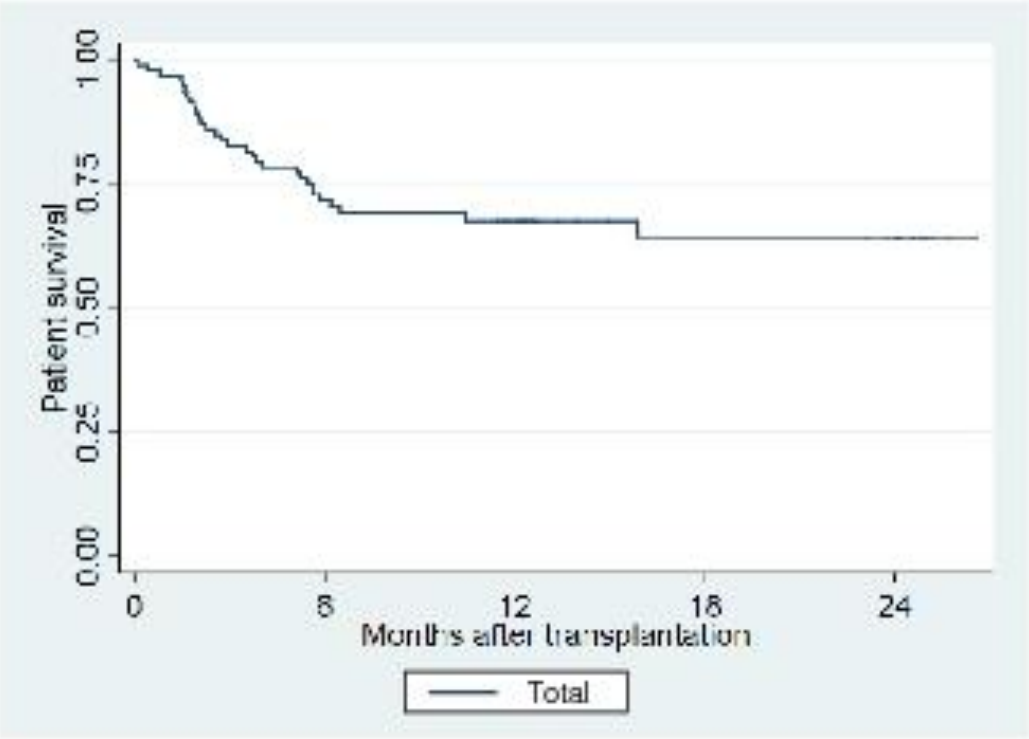
Still various outcomes

Table 2 Outcomes

Author, year	Ltx/total patients, n	Died before Ltx, n (%)	Type of bypass	Survival at 1 yr post-LTx, %	Length of stay post-LTx, days	MV, days post-LTx
Mason, 2010 [11]	51/51	na	na	50%	24 (9 to 55) H	na
Bermudez, 2011 [34]	14/17	3 (17%): neurologic dysfunction, thrombosis	VV, VA	74%	16 (3 to 40) ICU	12 (2 to 20)
Hammainen, 2011 [38]	13/16	3 (19%): septic MOF	VV, VA	92%	22 (3 to 63) ICU	na
Shafii, 2012 [41]	14/19	5 (26%): septic MOF 2, DIC 2, anoxic brain injury 1	VV, VA	75%	42 (19 to 175) H 15 (8 to 42) ICU	22 (5 to 125)
Nosotti, 2012	11/11	na	VV	87% and 50%[b]	47.6 ± 21.9 H 30 ± 20.4 ICU	27.1 ± 20.7
Javidfar, 2012 [20]	10/18[a]	8 (44%): pneumonia 1, MOF 6, CA 1	VV,VA	60%	22 (18 to 33) H 47 (41 to 52) ICU	na
George, 2012 [10]	122/122	na	na	57.6%	32 (16.5-60) H	na
Fuehner, 2012 [26]	20/26	6 (23%): CA 2, septic MOF 4	VV,VA	6-month 80%	38 (20 to 87) H 18 (1 to 69) ICU	14 (0 to 64)
Hoopes, 2013 [32]	31/31	na	VA, VV	93%	31 (12 to 86)[e] H	na
Anile, 2013 [36]	7/12	5 (41%)	VV, VA	85.7%	29 (15 to 59) H	<5
Toyoda, 2013 [33]	24/31	7 (22%)	VV,VA	74%	46 median H	na
Weig, 2013 [39]	13/26	13 (50%): acute liver failure 7, thoracic bleeding 3, cerebral hemorrhage 1,PE 2	VV,VA	54%	na	na
Crotti, 2013 [35]	17/25	8 (32%): MOF 3, septic shock 2, cardiogenic shock 2, intestinal ischemia 1	VV,VA	82% and 29%[c]	na	12.2 ± 11.9[d] 45.3 ± 33.5
Lafarge, 2013 [40]	30/36	6 (17%): GI bleeding 1, DIC 1, cerebral hemorrhage 1, CA 1, septic shock 1, therapeutic limitation 1	VV,VA,CPB	66.5%	na	na

Data are expressed as mean ± standard deviation or median and range. Mason *et al*., Nosotti *et al*., Hoopes *et al*. and George *et al*. enrolled transplanted patients. [a]Three of the eight patients who died had transiently recovered their baseline function and were weaned from ECMO support; they subsequently died before LTx. [b]ECMO group: 87% awake (7 pts); mechanical ventilation ECMO group: 50% (4 pts); [c]82% patients on ECMO bridge <14 days (early): 29% patients on ECMO bridge >14 days (late); [d]12.2 ± 11.9 days (early group) −45.3 ± 33.5 (late group). [e]Mean (range). LTx, lung transplant; CA, cardiac arrest; MOF, multi-organ failure; DIC, disseminated intravascular coagulation; GI, gastrointestinal; VV, veno-venous; VA, veno-arterial; CPB, cardiopulmonary by-pass; MV, mechanical ventilation; LOS, length of stay; H, hospital; na, not available.

Survival Rate of Recipients



	Total
At 6 months	73.5%
At 1 year	69.5%
At 2 years	65.6%

ASAIO Journal 2017

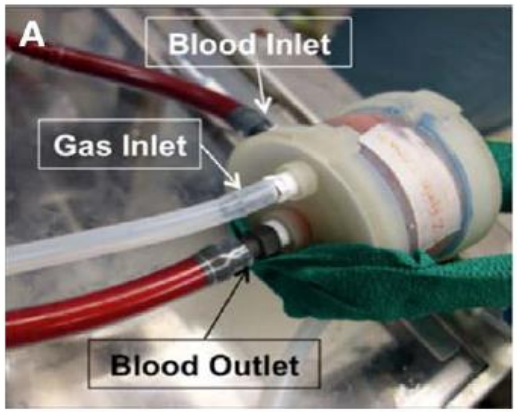
Pulmonary

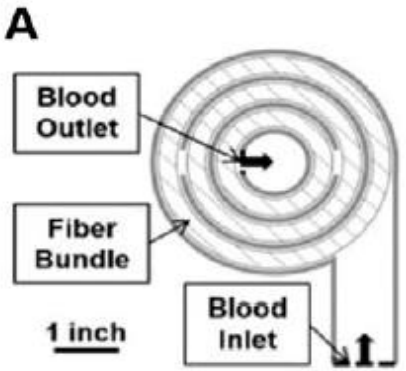
A Membrane Lung Design Based on Circular Blood Flow Paths

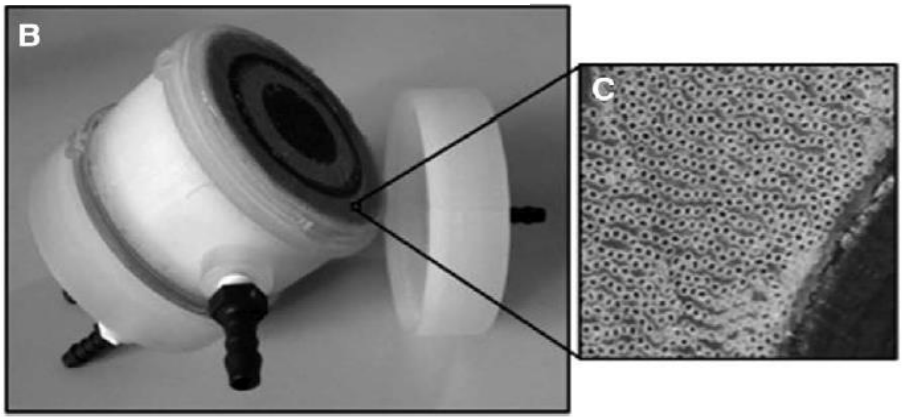
UDITHA PIYUMINDRI FERNANDO,*† ALEX J. THOMPSON,* JOSEPH POTKAY,* HANNAH CHERIYAN,* JOHN TOOMASIAN,* ANDREAS KAESLER,‡ PETER SCHLANSTEIN,‡ JUTTA ARENS,‡ RONALD B. HIRSCHL,* JOSEPH L. BULL,† AND ROBERT H. BARTLETT*

Current hollow fiber membrane lungs feature a predominantly straight blood path length across the fiber bundle, resulting in limited O_2 transfer efficiency because of the diffusion boundary layer effect. Using computational fluid dynamics and optical flow visualization methods, a hollow fiber membrane lung was designed comprising unique concentric circular blood flow paths connected by gates. The prototype lung, comprising a fiber surface area of 0.28 m^2, has a rated flow of 2 L/min, and the oxygenation efficiency is 357 ml/min/m^2. The CO_2 clearance of the lung is 200 ml/min at the rated blood flow. Given its high gas transfer efficiency, as well as its compact size, low priming volume, and propensity for minimal thrombogenicity, this lung design has the potential to be used in a range of acute and chronic respiratory support applications, including providing total respiratory support for infants and small children and CO_2 clearance in adults. *ASAIO Journal* 2017; 63:637–643.

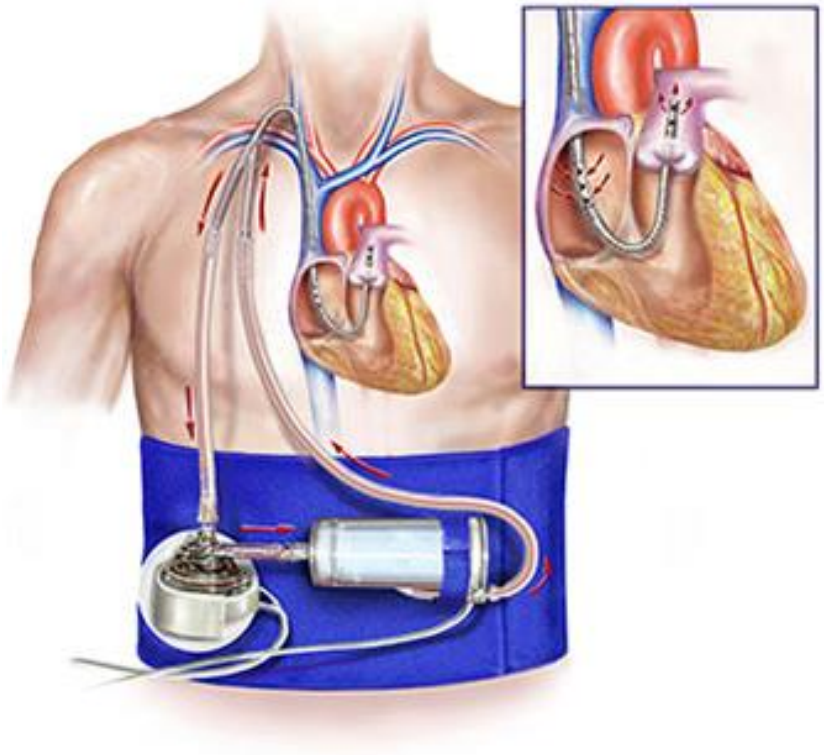
Key Words: artificial lung, circular flow, mixing, oxygenation



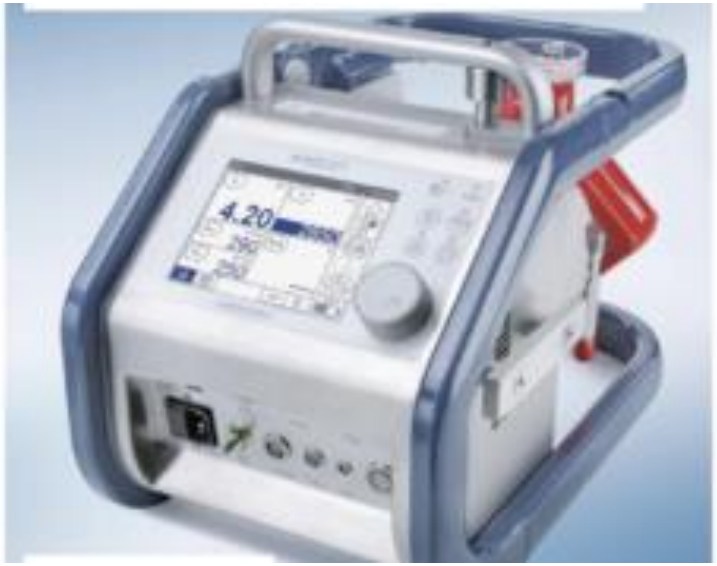




Wearable Membrane Lung



We need new device…



(연명의료 대상 의학적 시술 확대)	
Q6. **연명의료 대상 시술이** 확대된다는 데 어떻게 달라지나요?	A6. 개정 전 연명의료는 임종과정에 있는 환자에게 하는 **심폐소생술, 혈액투석, 항암제 투여, 인공호흡기 착용**의 의학적 시술로서 **치료효과 없이 임종과정의 기간만을 연장하는 것**으로 정의했습니다. 개정 후에는 **체외생명유지술(ECLS)***, **수혈, 혈압상승제 투여 및 그 밖에 담당의사가 환자의 최선의 이익을 보장하기 위해 시행하지 않거나 중단할 필요가 있다고 의학적으로 판단하는 시술**도 포함되어 다양한 의학적 시술에 대한 결정 근거가 마련되었습니다. 다만, 법 제19조제2항에 따라 연명의료중단등결정 이행 시 **통증완화를 위한 의료행위와 영양분 공급, 물 공급, 산소의 단순 공급**은 **유보·중단하지 않아야 한다**는 점에는 변경이 없습니다. * 체외생명유지술: 심각한 호흡부전·순환부전 시 체외순환을 통해 심폐기능 유지를 도와주는 시술(일반적으로 '체외형 막형 산화기(에크모, ECMO)'를 이용한 시술을 포괄하는 개념)

이행 내용	[ ] 심폐소생술 [ ] 인공호흡기 착용 [ ] 혈액투석 [ ] 항암제 투여 [ ] 체외생명유지술 [ ] 수혈 [ ] 혈압상승제 투여 [ ] 그 밖의 연명의료( )

When to initiate ECMO with low likelihood of success?

- When should ECMO NOT be offered (or should the line be drawn) ?

① Survival to discharge is NOT the sole most important outcome, BUT "good long-term survival

② Intensivists should NOT regard themselves as the sole arbiters and other variables should be considered such as institutional experiences, resources and polices

③ "Only those who will risk going too far can possibly find out how far it is possible to go."

Table 1 Checklist prior to initiating high-risk ECMO[a]

1. Is long-term survival with adequate neurological and functional recovery conceivable?
2. Does the institution currently have sufficient resources and expertise? If not, is referral to another centre feasible?
3. Is the institution ready to offer long-term support after ECMO, e.g. protracted ICU stay, transplantation, home ventilation?
4. Is the patient's family fully informed of the risks, do they understand the likely outcome and are they nonetheless supportive?
5. Is the ECMO leadership within the institution supportive?

If the answer to any of these questions is "no", then ECMO should be reconsidered.

ICU intensive care unit
ECMO extracorporeal membrane oxygenation
[a]ECMO which is not actively contraindicated but where survival to hospital discharge is unlikely

Overview of the four RCTs on ECMO in ARDS

	Study acronym	Sample size	Multicentre trial?	Primary endpoint	Significantly decreased mortality?*	Mortality in ECMO group	Mortality in control group	Major drawbacks
Zapol et al, 1979[3]	US-ECMO trial	90	Yes	Hospital survival	No	90%	92%	No lung-protective ventilation (Pmax >50 cm H_2O); high blood loss (2·5 L/day); inconsistent technique for extracorporeal blood flow; treatment could be stopped if after 5 days no improvement was observed
Morris et al, 1994[4]	..	40	No	30-day mortality	No	67%	58%	No lung-protective ventilation (Pmax >50 cm H_2O); high blood loss (4·7 L/day); fixed extracorporeal blood flow of 2·4 L/min
Peek et al, 2009[5]	CESAR	180	Yes	6-month mortality	Yes	37%	53%	Inconsistent ventilation; large proportion of patients without ECMO in ECMO group
Combes et al, 2018[8]	EOLIA	249	Yes	60-day mortality	No	35%	46%	Calculated with a very high relative risk reduction for mortality of 33% in ECMO group; terminated early for futility

ECMO=extracorporeal membrane oxygenation. Pmax=peak inspiratory airway pressure. *In ECMO group versus control group.

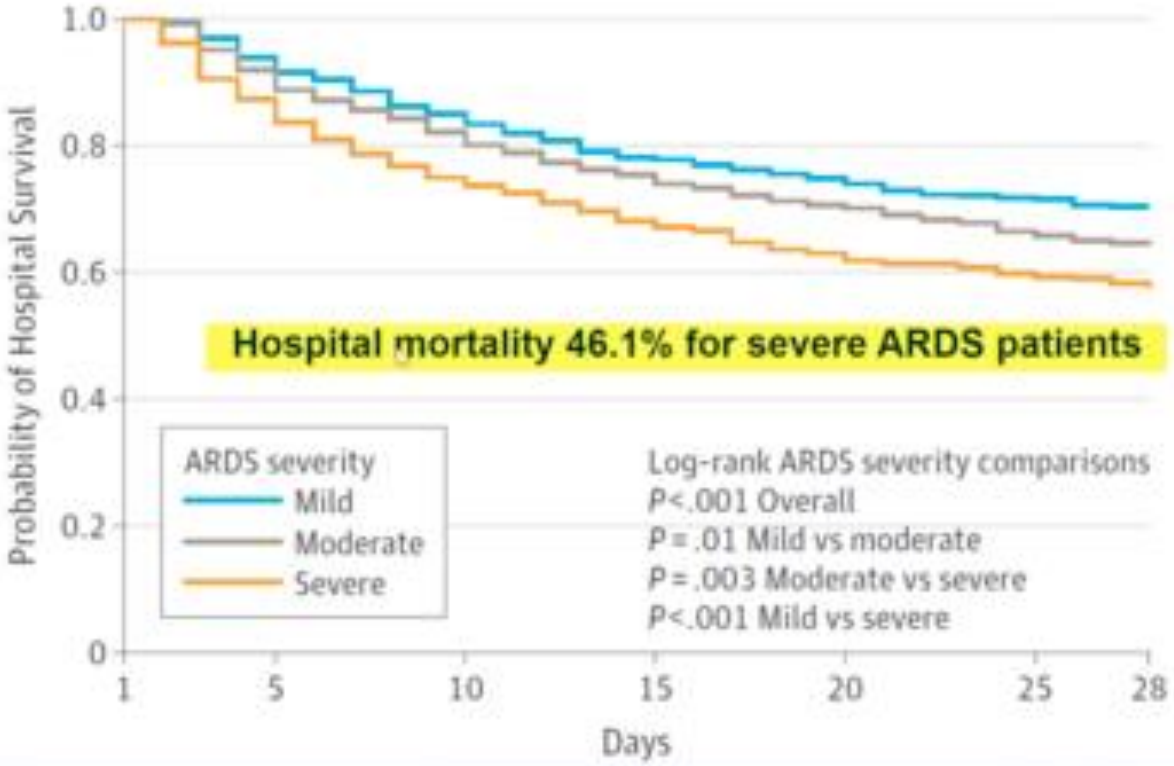
Table: **Overview of the four completed and published randomised clinical trials on ECMO in acute respiratory distress syndrome**

Is EOLIA trial negative?

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

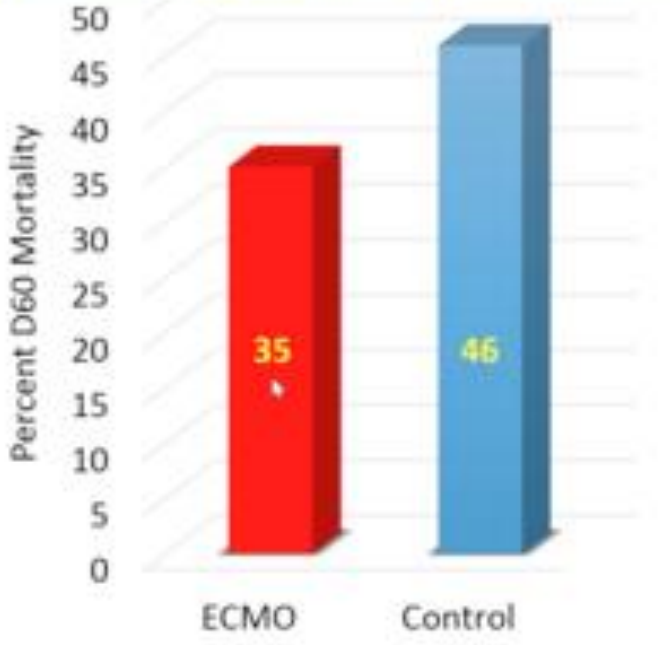
JAMA. 2016;315(8):788-800.

B Probability of hospital survival by ARDS severity

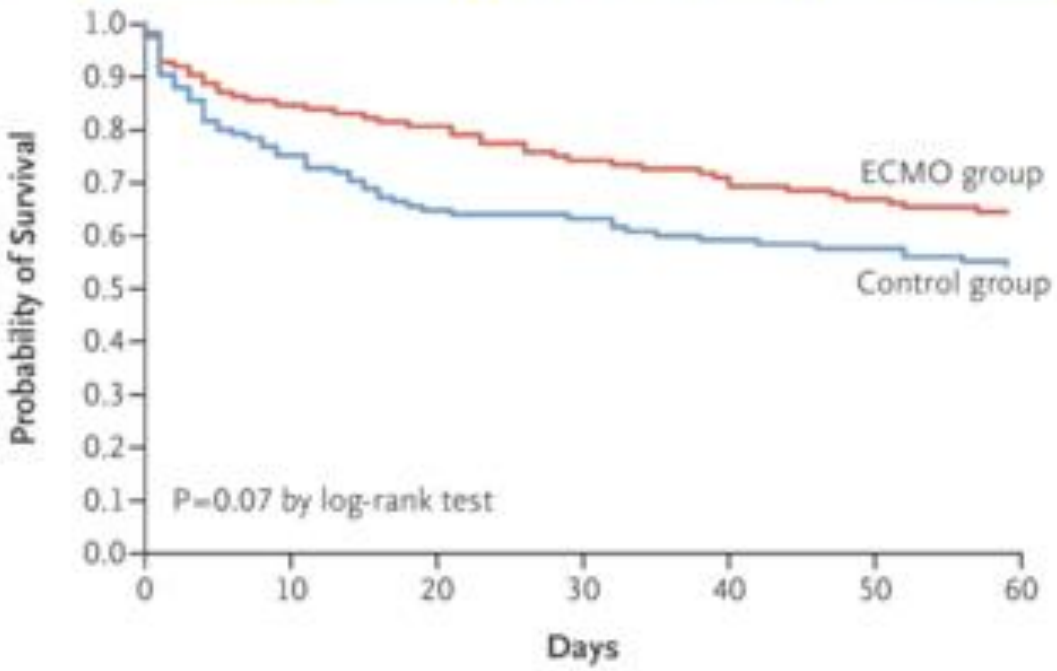


Primary Endpoint

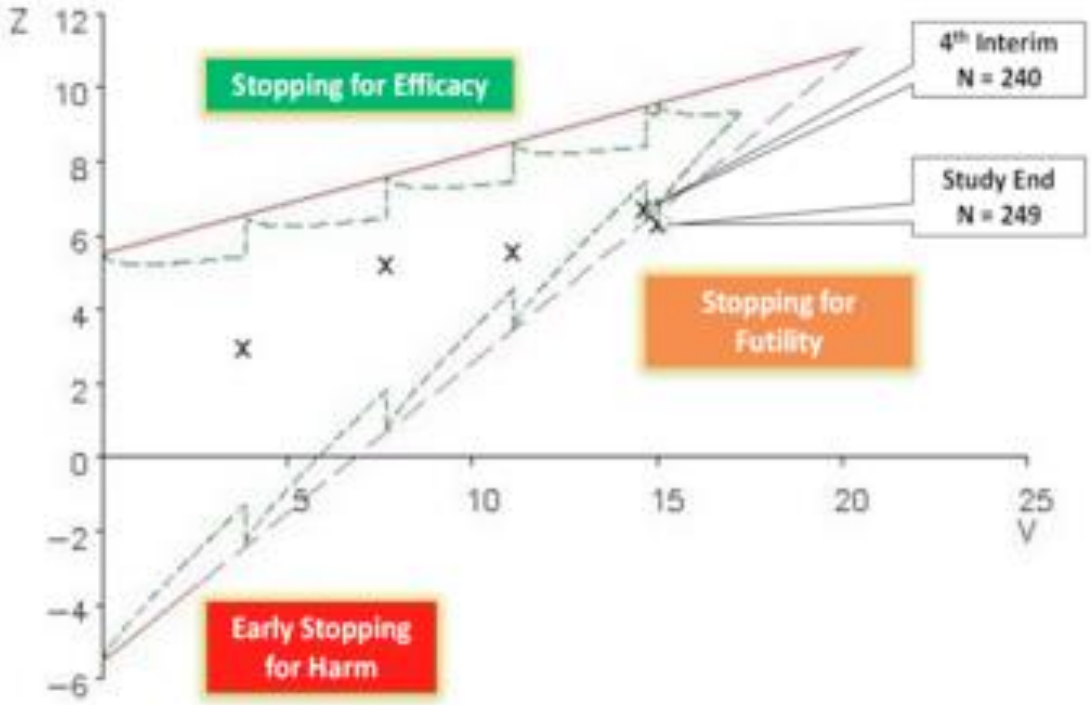
Relative Risk, 0.76, 95% CI, 0.55-1.04; P=0.087



Hazard Ratio, 0.70; 95% CI, 0.47-1.04, P=0.074 by log-rank test



Early termination of trial

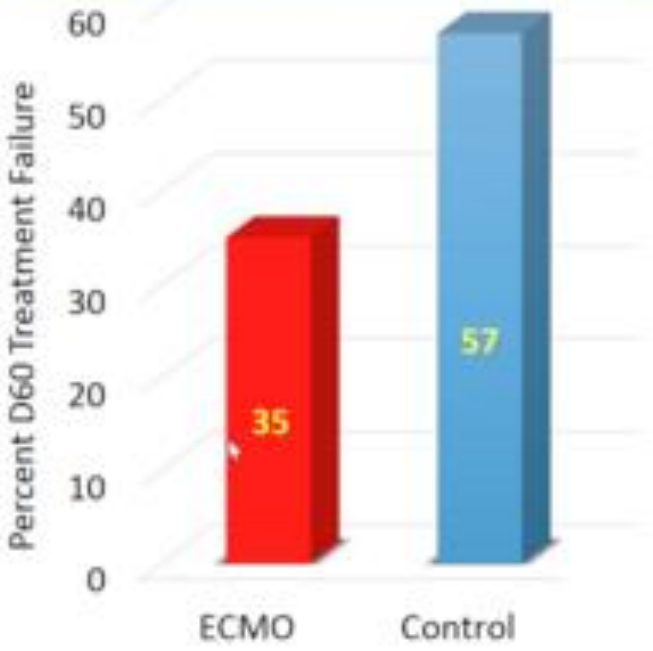


Date	V	Z	Value	Value	Recommendation
17/06/2013	3.83871	3.00000	-1.28389	5.43552	CONTINUE
17/07/2014	7.68242	5.24390	1.83463	6.47404	CONTINUE
08/09/2015	11.12134	5.59116	4.56222	7.46571	CONTINUE
11/04/2017	14.66642	6.70370	7.45432	8.40767	STOP TRIAL
27/11/2017	15.00779	6.29719	6.97416	9.25703	OVERRUNNING

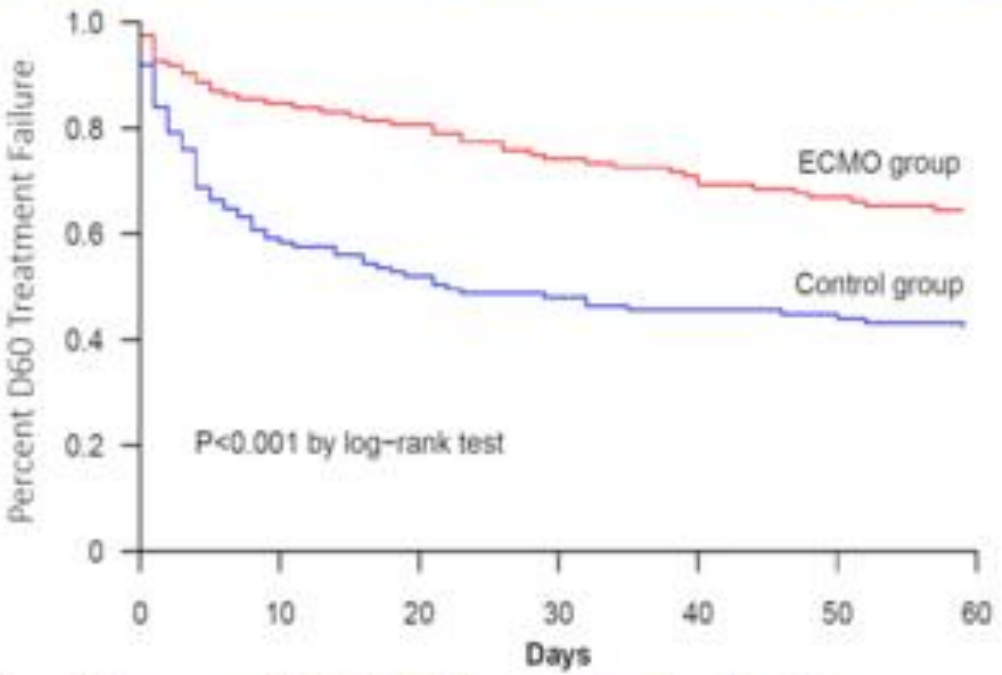
- Recruitment stopped
- At the 4th planned sequential interim analysis
  - 240 patients
  - April 2017
- Lower boundary of the stopping-rule triangle
  - Crossed
  - Predicting lack of difference

Key Secondary Endpoint

Relative Risk, 0.62; 95% CI, 0.47-0.82; P<0.001



Hazard ratio, 0.48; 95% CI, 0.34-0.70, P <0.001 by log-rank test



Death in ECMO group patients; Death or Crossover to ECMO in control patients

JAMA | Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial

Ewan C. Goligher, MD, PhD; George Tomlinson, MD, PhD; David Hajage, PhD; Duminda N. Wijeysundera, MD, PhD; Eddy Fan, MD, PhD; Peter Jüni, MD; Daniel Brodie, MD; Arthur S. Slutsky, MD; Alain Combes, MD, PhD

EDITORIAL

Time for Clinicians to Embrace Their Inner Bayesian?
Reanalysis of Results of a Clinical Trial of Extracorporeal Membrane Oxygenation

Roger J. Lewis, MD, PhD; Derek C. Angus, MD, MPH, FRCP

JAMA published online October 22, 2018

Is another RCT possible?

- During EOLIA period, an average enrolment rate of 0.058 patients/unit/month (i.e., less than 1 patients/unit/year).
- Calculations based on the characteristics of the patients in EOLIA show that **624 patients** would be required for a study with sufficient power to detect a significant 11% absolute mortality reduction in ECMO from 46% mortality of non-ECMO patients.
- With the enrolment rate of the CESAR trial (0.03 patients/unit/month) or the EOLIA trial(0.058 patients/unit/month) and 100 participating units, such a study would take 17 or 9 years, respectively.

Lessons from EOLIA

- ECMO does not kill patients
  - Emergency ECMO improves outcome by "buying time" in extremely hypoxemic patients.
  - ECMO improves outcome by reducing the invasiveness of mechanical ventilation.
- Bayesian analysis of post probability of mortality is benefit
  - Help to clarify the interpretation of "RCT" findings and how to apply in the "real world"
  - Early ECMO in very severe ARDS; Should be used promptly, NOT late rescue therapy (when death from ARDS or MOF is imminent)
- Should be managed in ECMO centers

Gattinoni et al. Critical Care 2018, Bartlett RH. Crit Care Med 2018, Combes A. EuroELSO 2019

Case Vignette from NEJM

- M/36, Severe ARDS
- Previous healthy, no medications, never smoker
- 1WA fever, chills, cough, G/W
- 2DA, DOE, urgent intubation at ER
- RAT for influenza +
- Initial lung protective ventilation, but worsening hypoxemia despite NMB, prone positioning
- ABGA: pH 7.22, pCO_2 62mmHg, pO_2 50mmHg

- What is the next option?

Treatment options

1. Recommend initiation of venovenous ECMO

2. Continue current treatment with other therapies

Poll

Which option would you choose?

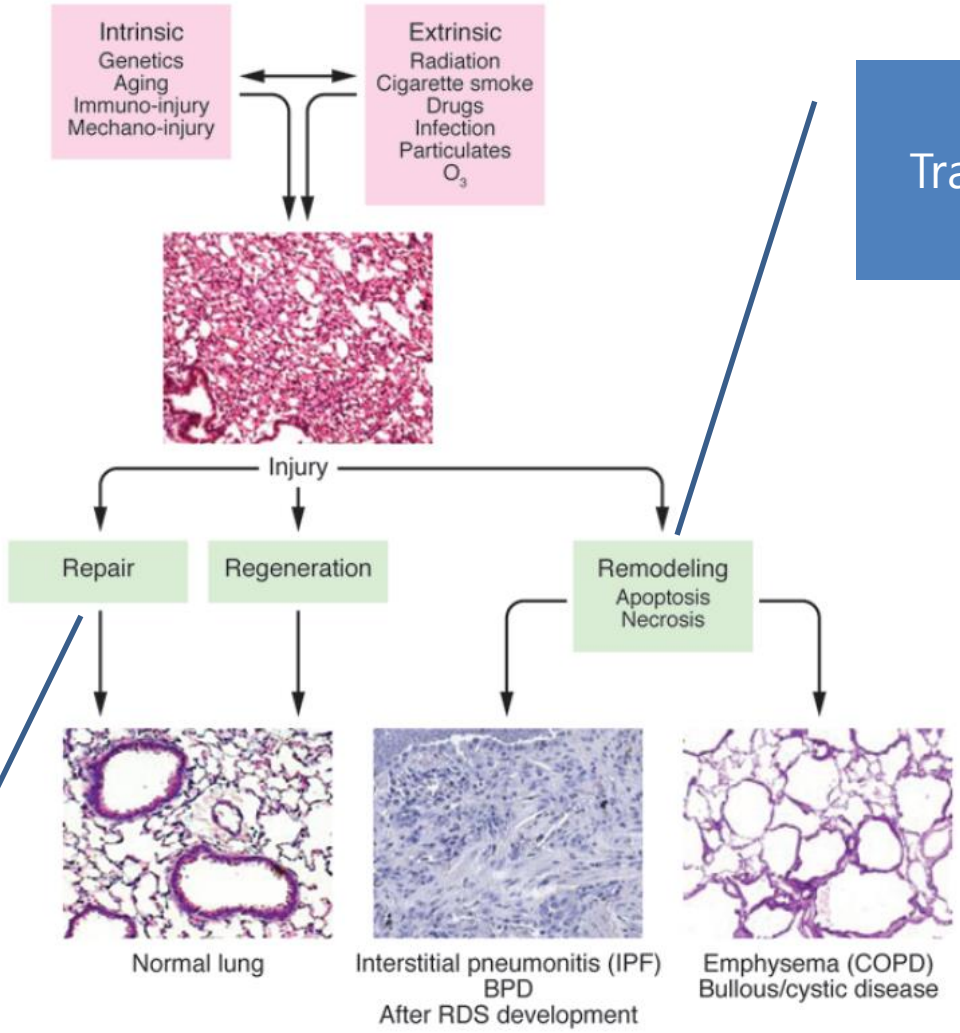
Recommend initiation of venovenous ECMO.	81%
Continue current treatment with other therapies.	18%

Back to Poll

3879 Total Responses

This open poll should not be interpreted as a scientifically valid physician survey.

Is ARDS reversible?



No recovery: Transplantation or POLST

Who is Reversible?

J Clin Invest 2011;121:2065

ORIGINAL ARTICLE

Reclassifying Acute Respiratory Distress Syndrome

Giorgia Maiolo[1], Francesca Collino[1], Francesco Vasques[1], Francesca Rapetti[1], Tommaso Tonetti[1], Federica Romitti[1], Massimo Cressoni[2], Davide Chiumello[2,3], Onnen Moerer[1], Peter Herrmann[1], Tim Friede[4], Michael Quintel[1], and Luciano Gattinoni[1]

[1]Department of Anesthesiology, Emergency and Intensive Care Medicine, University of Göttingen, Göttingen, Germany; [2]Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy; [3]Struttura Complessa Anestesia e Rianimazione, Azienda Socio Sanitaria Territoriale Santi Paolo e Carlo, Milan, Italy; and [4]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

Abstract

Rationale: The ratio of Pa_{O_2} to $F_{I_{O_2}}$ (P/F) defines acute respiratory distress syndrome (ARDS) severity and suggests appropriate therapies.

Objectives: We investigated *1*) whether a 150-mm-Hg P/F threshold within the range of moderate ARDS (100–200 mm Hg) would define two subgroups that were more homogeneous; and *2*) which criteria led the clinicians to apply extracorporeal membrane oxygenation (ECMO) in severe ARDS.

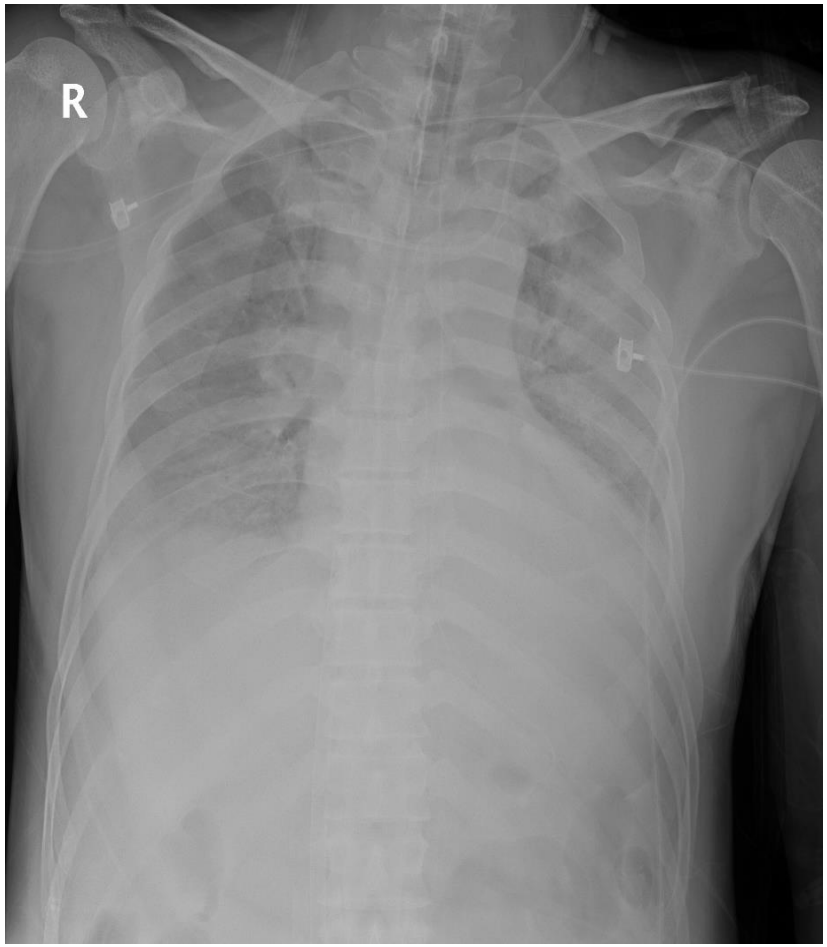
Methods: At the 150-mm-Hg P/F threshold, moderate patients were split into mild–moderate ($n = 50$) and moderate–severe ($n = 55$) groups. Patients with severe ARDS ($F_{I_{O_2}}$ not available in three patients) were split into higher ($n = 63$) and lower ($n = 18$) $F_{I_{O_2}}$ groups at an 80% $F_{I_{O_2}}$ threshold.

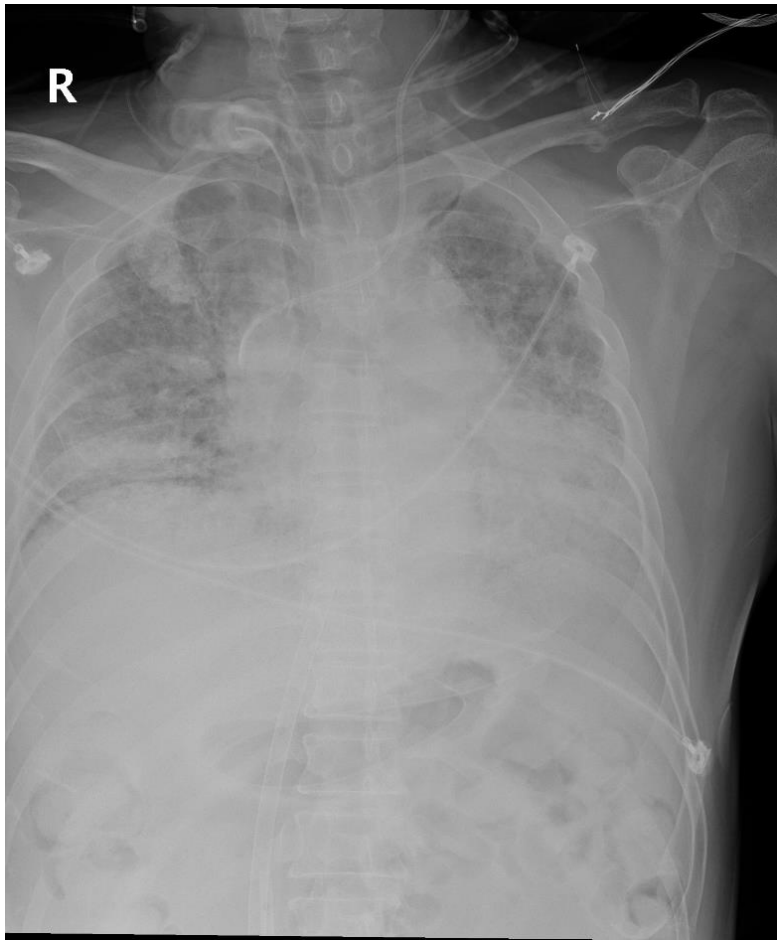
Measurements and Main Results: Compared with mild–moderate ARDS, patients with moderate–severe ARDS had higher peak pressures, Pa_{CO_2}, and pH. They also had heavier lungs, greater inhomogeneity, more noninflated tissue, and greater lung recruitability. Within 84 patients with severe ARDS (P/F < 100 mm Hg), 75% belonged to the higher $F_{I_{O_2}}$ subgroup. They differed from the patients with severe ARDS with lower $F_{I_{O_2}}$ only in Pa_{CO_2} and lung weight. Forty-one of 46 patients treated with ECMO belonged to the higher $F_{I_{O_2}}$ group. Within this group, the patients receiving ECMO had higher Pa_{CO_2} than the 22 non-ECMO patients. The inhomogeneity ratio, total lung weight, and noninflated tissue were also significantly higher.

Conclusions: Using the 150-mm-Hg P/F threshold gave a more homogeneous distribution of patients with ARDS across the severity subgroups and identified two populations that differed in their anatomical and physiological characteristics. The patients treated with ECMO belonged to the severe ARDS group, and almost 90% of them belonged to the higher $F_{I_{O_2}}$ subgroup.

Keywords: acute respiratory distress syndrome; mechanical ventilation; extracorporeal membrane oxygenation; lung inhomogeneity; computed tomographic analysis

M/65 (possible reversible), M/52 (bridge to lung TPL)





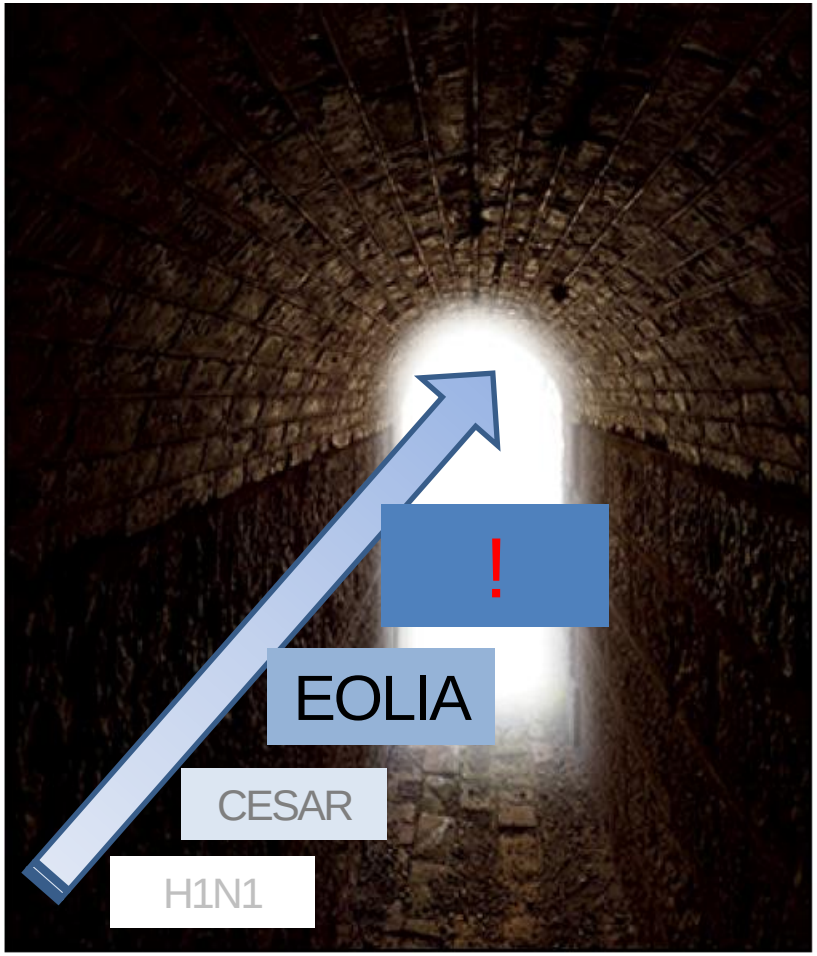
ASAIO Journal 2015

Prolonged VV ECMO (265 Days) for ARDS without Technical Complications

Arek J. Wiktor, MD, Jonathan W. Haft, MD, Robert H. Bartlett, MD, Pauline K. Park, MD, Krishnan Raghavendran, MD, and Lena M. Napolitano, MD

The patient remained neurologically fully intact with no evidence of hypoxic injury. Given her age and lack of pre-existing comorbidities, the patient and family requested continuation of all critical care support. She was able to tolerate moderate exercise with bicycle reconditioning. Chest computed tomography scans confirmed decreasing diffuse lung parenchymal consolidation consistent with resolving acute respiratory distress syndrome. Transient pulmonary hypertension (estimated right ventricle systolic pressure 73 mm Hg) required medical management; follow-up transthoracic echocardiogram showed an ejection fraction greater than 70% with hyperdynamic left ventricle, mild-to-moderate tricuspid regurgitation, right ventricular enlargement with moderately decreased right ventricular systolic function, and right ventricular systolic pressure of 37 mm Hg.

Serial evaluations were performed by the multidisciplinary lung transplant team for possible lung transplantation,[3,4] but she was not deemed a transplant candidate due to high panel reactive antibody (PRA) (93%) and possible pulmonary infection; desensitization therapy was also considered.[5] Infectious complications included enterococcus bacteremia and fungemia (*Candida parapsilosis*/glabrata); however, bronchoscopic alveolar lavage cultures demonstrated only mixed oral flora, and peripheral/ECMO circuit blood cultures were negative. No prophylactic antimicrobials were used.



Pixabay/makamuki0

"Statistics are an operational tool and not a religion; the knowledge, skill, and common sense of physicians are the values in the balance with "0.05"."


Thank you!

Another RCT?

- ECMO vs. Conventional : Unethical
- Tight definition of mortality risk in severe ARDS
  - New entry criteria considering the concept of VILI
- Two options
  - Very Early vs. Late rescue ECMO (already conducted in neonate 25 years ago)
  - ECMO with awake and/or ambulatory vs. heavy sedation/paralysis