The Intensive Connection

Acute Respiratory Failure: ECLS

Table of Contents

Acute Respiratory Failure ECLS

Current Status 2017

Completed

This module is updated and maintained by the Acute Respiratory Failure section

Latest Update

First Edition

Acute Respiratory Failure

Chair

Jordi Mancebo MD, *Director, Intensive Care Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Chair of Acute Respiratory Failure Section, ESICM*

Deputy

Luigi Camporota MD, PhD, FRCP, FFICM, *Consultant Intensivist at Guy's and St. Thomas' NHS Foundation Trust, London, Greater London, United Kingdom*

Section Editor

Hadrien Roze MD, *South Department of Anesthesiology and Intensive Care Médicine Thoracic ICU Bordeaux University Hospital France*

ELearning Committee

Chair

Kobus Preller Dr., *Consultant, John Farman ICU, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

Deputy

Mo Al-Haddad MD, *Consultant in Anaesthesia and Critical Care, Queen Elizabeth University Hospital; Honorary Clinical Associate Professor University of Glasgow, Glasgow UK*

Project Manager

Estelle Pasquier , *European Society of Intensive Care Medicine*

First Edition 2016

Module Authors

Laveena Munshi MD, *Interdepartmental Division of Critical Care Medicine University of Toronto Toronto, Ontario, Canada*

Eddy Fan MD, *Interdepartmental Division of Critical Care Medicine University of Toronto Toronto, Ontario, Canada*

Alberto Goffi MD, *Interdepartmental Division of Critical Care Medicine University of Toronto Toronto, Ontario, Canada*

Lorenzo Del Sorbo Dr., *Interdepartmental Division of Critical Care Medicine University of Toronto Toronto, Ontario, Canada*

Michele Umbrello MD, *SC Anestesia e Terapia Intensiva, Asst Santi Paolo e Carlo - Ospedale San Paolo. Polo Universitario, Università degli studi di Milano.Via A. Di Rudinì 8, 20142, Milan-Italy*

Paolo Formenti MD, *SC Anestesia e Terapia Intensiva, Asst Santi Paolo e Carlo - Ospedale San Paolo. Polo Universitario, Università degli studi di Milano.Via A. Di Rudinì 8, 20142, Milan-Italy*

Module Reviewers

Davide Chiumello MD, *Director, Department of Anaesthesia and Intensive Care, San Paolo Hospital - ASST Santi Paolo e Carlo, Milan, Italy; Professor, Department of Health Science, University of Milan, Milan, Italy*

Mo Al-Haddad MD, *Consultant in Anaesthesia and Critical Care, Queen Elizabeth University Hospital; Honorary Clinical Associate Professor University of Glasgow, Glasgow UK*

Section Editor

Davide Chiumello MD, *Director, Department of Anaesthesia and Intensive Care, San Paolo Hospital - ASST Santi Paolo e Carlo, Milan, Italy; Professor, Department of Health Science, University of Milan, Milan, Italy*

CoBaTrICE Mapping Contributors

Cristina Santonocito MD, *Dept. of Anesthesia and Intensive Care, IRCSS-ISMETT-UPMC, Palermo, Italy*

Victoria Anne Bennett MD, *St George's Hospital, London, United Kingdom*

Co-Ordinating Editor

Stephanie C. Cattlin MBBS, Bsc, FRCA, FFICM, *Consultant in Intensive Care, Imperial College Healthcare NHS Trust, London, UK*

Executive Editor

Mo Al-Haddad MD, *Consultant in Anaesthesia and Critical Care, Queen Elizabeth University Hospital; Honorary Clinical Associate Professor University of Glasgow, Glasgow UK*

Update Info

Learning Objectives

After studying this module on ExtraCorporeal Life Support (ECLS) in Acute Respiratory Distress Syndrome (ARDS) patients, you should be able to:

1. Describe the PHYSIOLOGY of ECLS
2. List the major INDICATIONS and associated CONFIGURATIONS of ECLS
3. Outline the role of ECLS for ARDS, Obstructive Lung Disease and a Bridge to Lung Transplant in terms of :
    1. Configurations and trouble shooting the circuit
    2. Clinical evidence
    3. Clinical management and controversies
4. List patient and circuit associated COMPLICATIONS

eModule Information

Expiry date: 10/2020

COBATrICe competencies covered in this module:

Competencies

- Recognises and manages the patient with acute respiratory failure and ARDS
- Describes the use of devices for circulatory or respiratory assist

Faculty Disclosures:
The authors of this module have not reported any disclosures.

Duration: 8 hours

1. Introduction

Extracorporeal life support (ECLS) is a means to improving oxygenation, ventilation and hemodynamic support using an extracorporeal circuit comprised of an oxygenator and a centrifugal pump. Traditionally, its indications have spanned refractory hypoxemic or hypercapnic respiratory failure, and cardiogenic shock. Over the years, substantial advancements in the technology have resulted in an increase in safety and minimised the complexity associated with its use.

Recent evidence suggests possibe favourable outcomes associated with the use of ECLS for severe acute respiratory failure; however, there are limited data from large, randomised controlled trials to confirm efficacy. Therefore, more evidence will be needed to guide clinicians on its role in patients with severe acute respiratory failure.

This module will focus primarily on ECLS for hypoxemic and hypercapnic respiratory failure.

Note

Potential applications for ECLS:
Hypoxemia
Hypercapnia
Cardiogenic shock
Significant technologic advancements have renewed enthusiasm for the role of ECLS in adults with respiratory failure

2. Physiology of gas exchange

2. 1. The ECLS Circuit

Extracorporeal circuits use a centrifugal pump to aspirate or drain de-saturated venous blood from a large central vein (e.g. IVC via the femoral vein or SVC via the internal jugual vein). The venous blood is pumped to the oxygenator where gas exchange occurs. Modern oxygenators (also referred to as an artificial lung or gas exchange device) are composed of hollow fibres that separate the blood and gas phase. Blood flows around the hollow fibres while sweep gas (either 100% oxygen or air/oxygen mix) is delivered through the hollow fibres. Oxygen uptake and carbon dioxide removal occurs across the walls of these fibres. Oxygenated and de-carboxylated blood is then returned to the patient.

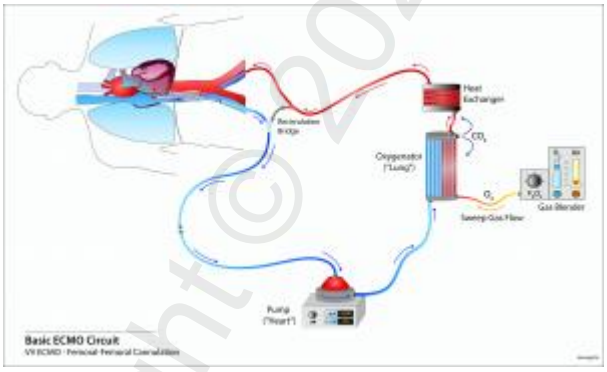

Figure 1: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Review. Image by Alberto Goffi

2. 2. Oxygenation

The **single** most important factor in oxygen uptake by the oxygenator is ECLS blood flow. This is a consequence of the unique mode of oxygen carriage by haemoglobin. Once haemoglobin is fully saturated, further oxygen uptake can only be achieved by continued delivery of de-saturated haemoglobin to the oxygenator. Dissolved oxygen provides minimal contribution to overall oxygen uptake.

Diffusion of oxygen through the walls of the hollow fibres could be compromised in case of thrombus formation or excessive fibrin deposition. However, even in the presence of visible clot in the oxygenator, most contemporary oxygenators perform satisfactorily for many days.

Oxygen delivery is the product of cardiac output and oxygen content. Oxygen content is composed of haemoglobin, oxygen saturation, and a dissolved component of oxygen.

- Oxygen delivery = cardiac output x oxygen content
- Oxygen content = (Hb x SaO_2 x 1.34) + (0.003 x PaO_2)

The major factors in determining oxygen uptake via oxygenator include the following:

- **ECLS blood flow**
- Oxygen saturation of pre-oxygenator blood
- Haemoglobin concentration
- Diffusion of oxygen through hollow fibres

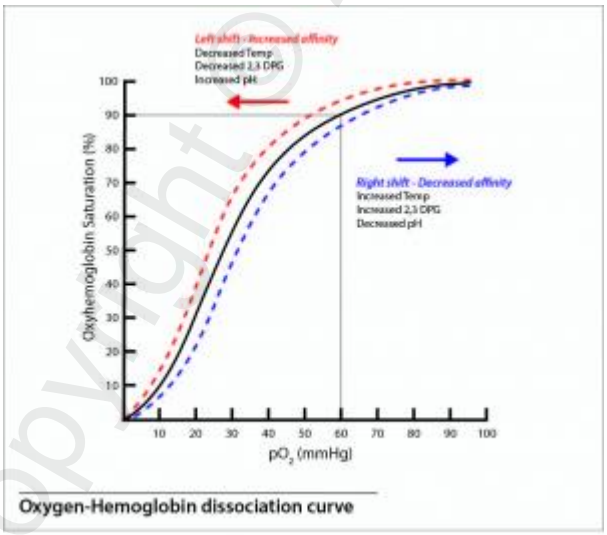

Figure 2: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Review
Illustration by Alberto Goffi

2. 3. Carbon Dioxide Removal

Carbon dioxide is dissolved in blood and its removal by the oxygenator is characterised by a linear and steep dissociation curve. The high solubility of carbon dioxide in blood allows for very efficient CO_2 removal by the oxygenator.

The major factors in determining blood CO_2 removal via ECLS include the following:

- Sweep Gas Flow
- Surface area of oxygenator
- Diffusibility through microfibers (could become compromised in the presence of clots or excessive fibrin deposition)
- Blood flow

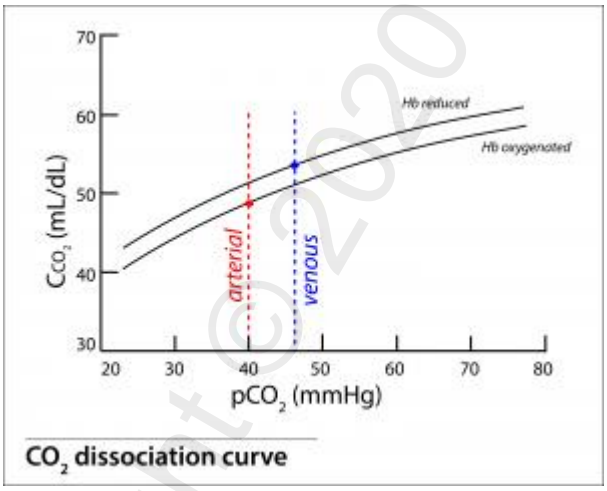

Figure 3: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Review
Illustration by Alberto Goffi

3. Indications

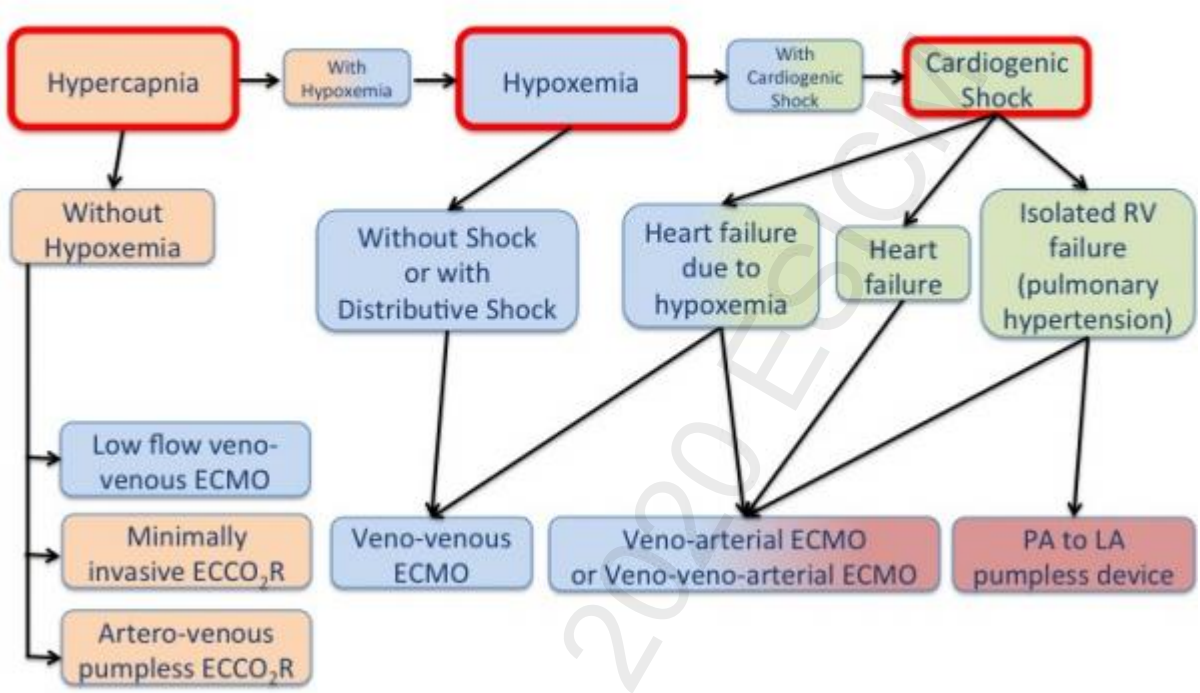

Figure 4: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

3. 1. Indications: Hypoxemia

ECLS acts as an oxygenating shunt for hypoxemia refractory to conventional mechanical ventilation as a bridge to recovery. Causes of hypoxemia may include the following:

- Acute Respiratory Distress Syndrome (ARDS)
- Acute Pulmonary Embolism
- Other reversible causes of acute respiratory failure (e.g., acute eosinophilic pneumonia, alveolar haemorrhage)
- Primary Graft Dysfunction following Lung Transplant

Evidence-based thresholds to guide initiation ECLS for hypoxemia have not been established. Current indications suggested by the Extracorporeal Life Support Organization (2009) include the following:

- Consider if risk of mortality is 50% or greater (e.g., PaO_2/FiO_2 90 mmHg and/or Murray Score 2-3)
- Indicated when risk of mortality is 80% or greater (e.g., PaO_2/FiO_2 90 mmHg and a Murray Score 3-4)

Table 1:

Murray score	**0**	**1**	**2**	**3**	**4**
CXR(quadrants with consolidation)	n. 0	n. 1	n. 2	n. 3	n. 4
Hypoxemia (PaO_2/FiO_2)(mmHg)	≥300	225-299	175-224	101-174	≤100
PEEP (cmH_2O)	<5	6-8	9-11	12-14	>15
Compliance (ml/cmH_2O)	>80	60-79	40-59	20-39	<19
The final score is calculated by the addition of the component parts divided by 4					

These simply provide a framework for when to consider ECLS. Various organisations have established their own thresholds when to initiate or refer for ECLS. Indications for ECLS for ARDS from 3 recent studies are outlined below

Table 2:

Peek 2009 (UK)1	**ECMO net 2011 (Italy; H1N1)2**	**Pham 2013 (France; H1N1)3**
Age 18-65 years old Severe but potentially reversible respiratory failure (Murray score >3.0 or pH <7.2)	Oxygenation Index >30 PaO_2/FiO_2 <70 mmHg with PEEP >15 cmH_20 at ECMO centre PaO_2/FiO_2 <100 mmHg with PEEP >10 cm H_20 awaiting transfer pH <7.25 for at least 2 hours and haemodynamic instability	PaO_2/FiO_2 <50mmHg, despite PEEP 10-20cmH_20 and FiO_2 >0.80 or Plateau pressures > 35cmH_20, despite attempts to reduce tidal volumes to <4ml/kg

3. 2. Modalities: Hypoxemia

Veno-venous ExtraCorporeal Membrane Oxygenation (ECMO) is the configuration of choice for hypoxemic respiratory failure.

If concomitant shock exists and the shock is attributed to right ventricular dysfunction in the context of ARDS, haemodynamics may improve with the application of veno-venous ECMO given the rapid reversal of hypoxemic vasoconstriction and drop in pulmonary vascular resistance.

If vasodilatory shock complicates respiratory failure in the context of sepsis, veno-venous ECMO would remain the modality of choice with the employment of vasopressors for vasodilation.

When the origin of shock associated with respiratory failure is due to left ventricular or biventricular failure resulting in end organ hypoperfusion, veno-arterial or a hybrid veno-veno-arterial ECMO may be the modality of choice.

Refer to section on Configurations for more details.

3. 3. Indications: Hypercapnia

ECLS acts as a CO_2 removal circuit for hypercapnic respiratory failure refractory to conventional therapies or mechanical ventilation as a bridge to recovery. Causes of hypercapnia may include the following:

- Acute Respiratory Distress Syndrome (ARDS)
- Obstructive Airway Disease:
    - Chronic obstructive pulmonary disease (COPD)>
    - Severe asthma/status asthmaticus
    - Bronchiolitis obliterans syndrome (BOS)
    - Cystic fibrosis

Definitive thresholds to guide initiation of ECLS for hypercapnia have not yet been established. Current indications suggested by the Extracorporeal Life Support Organization (2009) include the following:

- CO2 retention due to asthma or permissive hypercapnia with a $PaCO_2$ >80 mmHg or inability to achieve safe inflation pressures (Pplat $\geq$ 30 cm H_20)

3. 4. Modalities: Hypercapnia

A series of different ECLS configurations can be employed for hypercapnic respiratory failure:

Veno-venous ECMO: Veno-venous ECMO is useful if concomitant hypoxemia and hypercapnia are the indication for ECLS.

In the body CO_2 is produced at the rate of about 200-250 mL/min, and in normal conditions the venous blood (pH 7.38 and $PaCO_2$ 45 mmHg) contains about 500 mL/L of CO_2. Therefore, 0.5-1 L/min (low flow) ECMO blood flow through the artificial lung, provided with adequate sweep gas flow (> 6L/min), can theoretically remove the entire volume of CO_2 produced. In this setting, ECMO blood flow is low and therefore oxygen uptake is limited.

Low flow veno-venous extracorporeal carbon dioxide removal (VV $ECCO_2R$) is similar to VV EMO but uses smaller single or dual-lumen cannulae, a low resistance oxygenator and blood pump. The low ECLS blood flows achieved with these systems provide satisfactory CO2 removal but limited oxygen uptake. (see Physiology of Gas Exchange)

Arterio-venous extracorporeal CO_2 removal devices (pumpless or AV $ECCO_2R$) rely on the patient's arterial pressure to drive blood flow through the oxygenator. The usual configuration of AV $ECCO_2R$ is using small cannulae in the femoral artery and vein. Similar to VV $ECCO_2R$ systems, the low extracorporeal blood flow achieved in AV $ECCO_2R$ provides satisfactory CO_2 clearance with limited oxygen uptake.

Extracorporeal CO_2 removal ($ECCO_2R$) devices: $ECCO_2R$, similar to haemodialysis, employs a single venous dual-lumen catheter and low extracorporeal blood flow through the gas exchanger. Similar to the arterio-venous interventional lung assist, it does not provide significant oxygenation due to the low blood flow rates. (Refer to section on Configurations for more details)

3. 5. Contraindications

Absolute contraindications:

- Any critical co-morbid conditions preventing bridge to meaningful recovery (e.g., metastatic cancer, catastrophic neurologic injury)

Potential relative contraindications include the following:

- Any significant contraindication to heparinisation (e.g., central nervous system haemorrhage, heparin induced thrombocytopenia, major bleeding not amenable to treatment/reversal)
- Prolonged exposure to injurious mechanical ventilation (>7-10 days), given the high likelihood of ventilator-associated lung injury
- An irreversible cause of respiratory failure and not a candidate for lung transplant

The nature (absolute or relative) of these contraindications may vary from centre to centre

4. Configurations

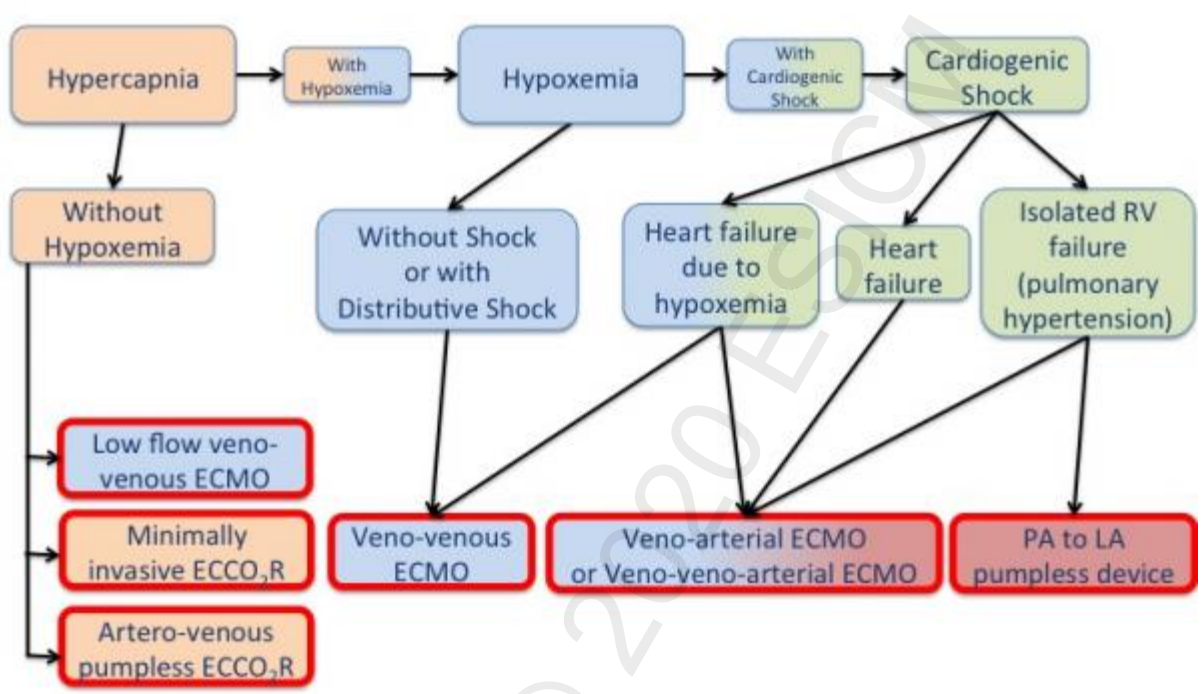

Figure 5: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

4. 1. Veno-venous Extracorporeal Membrane Oxygenation

For veno-venous ECMO, venous blood is drained from a large central vein (inferior vena cava via the femoral vein or superior vena cava via the internal jugular vein). Blood is pumped through the oxygenator and returned to the superior vena cava/right atrium via the internal jugular or inferior vena cava via femoral vein.

Femoral-femoral, femoral-internal jugular or the bicaval dual-lumen internal jugular catheter are possible veno-venous ECMO configurations.

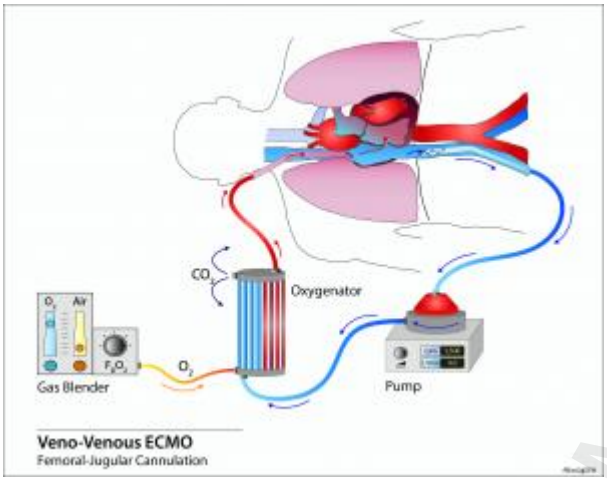

Figure 6: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

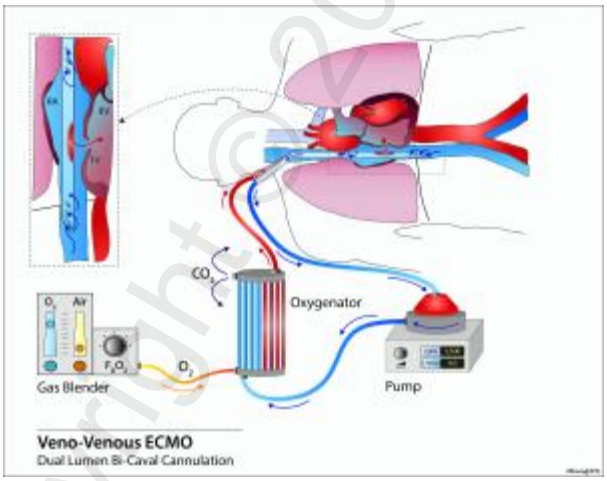

Figure 7: Illustration by Alberto Goffi

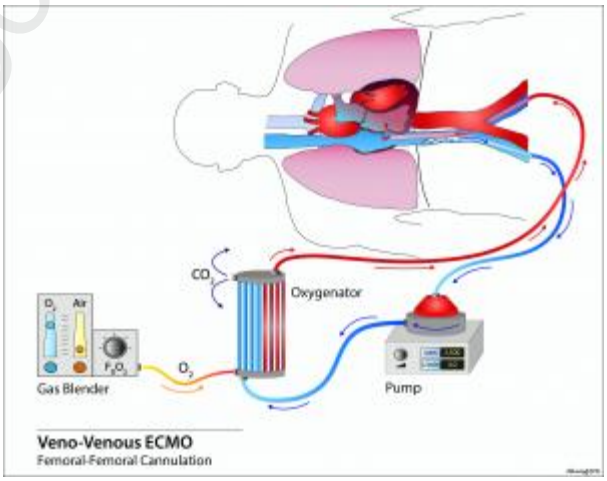

Figure 8: Illustration by Alberto Goffi

4. 2. Veno-arterial Extracorporeal Membrane Oxygenation

In the setting of respiratory failure with concomitant cardiogenic shock, veno-arterial ECMO, may be the configuration of choice. Venous blood is drained from a large central vein (often the inferior vena cava via the femoral vein). Blood is pumped through the oxygenator and returned to the arterial circulation via the contra-lateral femoral artery.

However, during this form of peripheral VA ECMO, fully oxygenated blood from the ECMO circuit is delivered retrograde to the distal aorta via the femoral artery and in the presence of continued native lung dysfunction, de-oxygenated blood maybe ejected into the proximal aorta from the left ventricle (LV) and pulmonary circulation. The level in the aorta at which these two sources of blood mix is determined by extent of left ventricular dysfunction. When LV function is minimal, fully oxygenated blood from the ECMO circuit is pumped back up to the level of the aortic valve. If LV ejection is preserved, poorly oxygenated blood from the dysfunctional native lungs may be delivered to the proximal aorta (coronary and cerebral circulation).

In these circumstances, veno-arterial-venous (VA-V) ECMO may alleviate this problem. In VA-V configuration, de-saturated venous blood is drained from the IVC via the femoral vein and oxygenated blood is returned to two sites, the contra-lateral femoral artery and to the SVC. Oxygenated blood is delivered to the distal aorta but also to the pulmonary circulation to improve oxygenation of blood ejected into the proximal aorta. If LV function remains stable, consideration should be given to changing from VA-V to VV ECMO for continued native lung dysfunction.

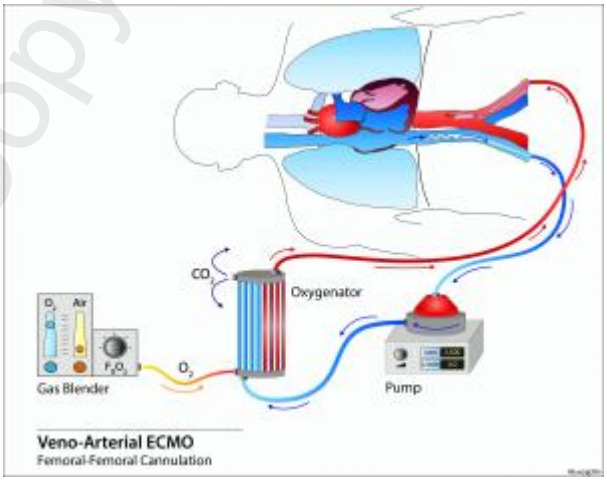

Figure 9: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan

E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

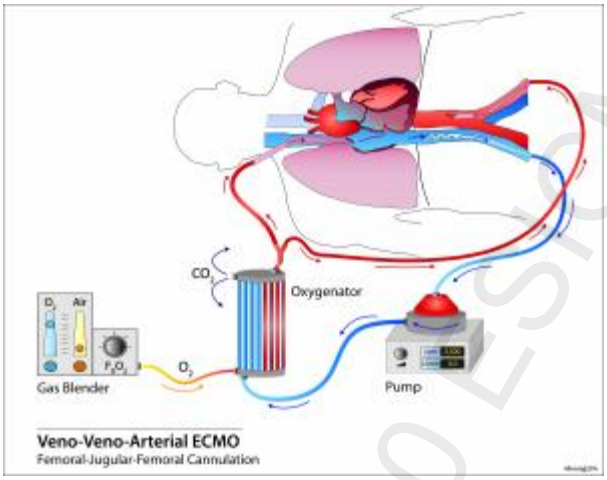

Figure 10: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

4. 3. Extracorporeal CO Removal

The three modalities available for isolated CO_2removal:

Extracorporeal CO_2 removal devices employs a single venous dual-lumen catheter (internal jugular or femoral vein) and low flow extracorporeal blood flow that is pumped through a gas exchanger.

Low flow VV ECCO_2R uses a single dual-lumen cannula in the internal jugular vein. Low blood flow is maintained through the oxygenator using a low capacity centrifugal pump. This configuration has been used to facilitate mobilisation/ambulation of the patient.

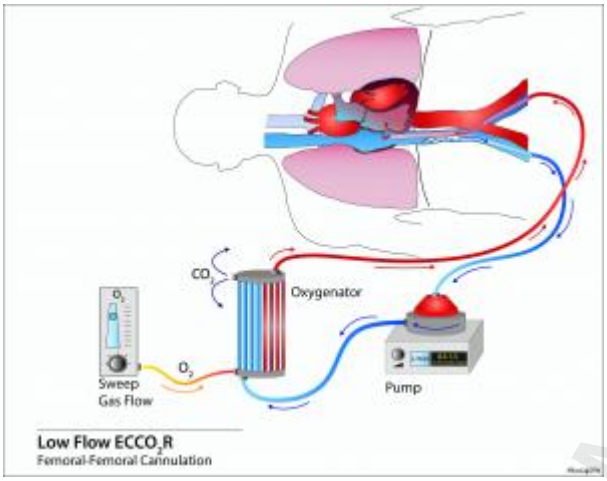

Figure 12: Extracorporeal carbon dioxide removal (ECCO2R) in patients with acute respiratory failure. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Intensive Care Med. 2017 Apr;43(4):519-530. doi: 10.1007/s00134-016-4673-0. Epub 2017 Jan 28. Illustration by Alberto Goffi

Low flow veno-venous ECMO is similar to veno-venous ECMO with the exception of the employment of smaller cannula leading to a limited amount of flow through the ECMO circuit.

Low flow VV ECCO$_2$R uses a small single-lumen cannula in each femoral vein. Low blood flow is maintained through the oxygenator using a low capacity centrifugal pump.

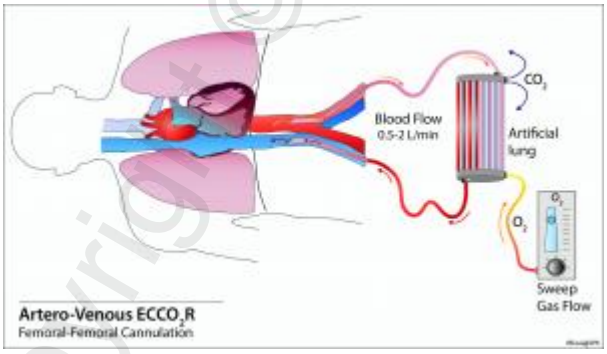

Figure 13: Extracorporeal carbon dioxide removal (ECCO2R)in patients with acute respiratory failure. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Intensive Care Med. 2017 Apr;43(4):519-530. doi: 10.1007/s00134-016-4673-0. Epub 2017 Jan 28. Illustration by Alberto Goffi

Arterio-venous interventional lung assist is a pumpless form of ECMO that relies on the arterio-venous pressure difference to facilitate flow through a gas exchanger. It employs smaller cannula and can easily facilitate CO_2removal.

Arterio-venous $ECCO_2R$ uses a small femoral arterial and venous cannula. The patient's arterial-venous pressure difference pumps blood through the gas exchanger.

4. 4. PA to LA pumpless device

This configuration has been described in small case series of patients with primary pulmonary hypertension awaiting lung transplantation but who develops life threatening failure of the right ventricle (RV). After sternotomy, a surgically placed cannula in the pulmonary artery trunk is connected to a left atrial cannula using the same low resistance gas exchange device employed in peripherally placed AV $ECCO_2R$ system (see above). The extracorporeal shunt immediately decompresses the failing RV. Gas exchange is achieved by a combination of extracorporeal CO2 elimination and continued perfusion/ventilation of native lungs.

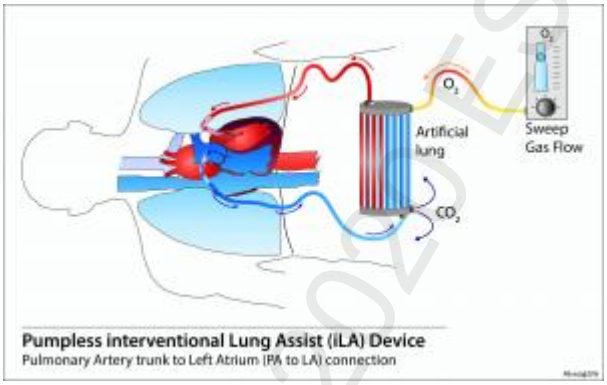

Figure 14: Extracorporeal carbon dioxide removal (ECCOR) in patients with acute respiratory failure. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Intensive Care Med. 2017 Apr;43(4):519-530. doi: 10.1007/s00134-016-4673-0. Epub 2017 Jan 28. Illustration by Alberto Goffi

Table 3: depicts the configurations and settings of the different ECLS modalities available

VV-ECMO Veno-venous by pass, in series with pulmonary circulation	**Circuit/bypass**	**$ECCO_2R$ Veno-venous by pass, in series with pulmonary circulation**
from central vein (IJ, FV, SV)	Blood drainage	from central vein (IJ, FV, SV) or Fem artery in AV configuration
into right atrium	Blood return	into central vein (IJ, FV, SV)
16 -31 Fr	Cannula	8-29 Fr
Single or Double	Intravascular	Single or Double

Two single cannulas or dual-lumen cannula	Cannula type	Two single cannulas or dual-lumen cannula
Centrifugal	Pump	Centrifugal or peristaltic
2-7 L/min	Extracorporeal Blood Flow	0.2-2.0 L/min
100% VCO_2	CO_2 clearance	10-100% VCO_2 dependent mainly on sweep gas flow
dependent	Oxygen delivery capacity	not significant

Abbreviations:

- FV = femoral vein
- IJ = internal jugular vein
- SV = subclavian vein
- Fr = French

5. Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome

References found in this Chapter

(Peek et al. 2009; Pappalardo et al. 2013; Pham et al. ; Zapol et al. 1979; Noah et al. 2011; Bein et al. 2013; Schmidt et al. 2013; Terragni et al. 2007; Terragni et al. 2009; Madjdpour et al. 2003; Bellani et al. 2011; Kilgannon et al. 2010; Mikkelsen et al. 2012; Del Sorbo, Cypel and Fan. 2014)

References

- Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration., Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial., 2009, PMID:19762075
- Pappalardo F, Pieri M, Greco T, Patroniti N, Pesenti A, Arcadipane A, Ranieri VM, Gattinoni L, Landoni G, Holzgraefe B, Beutel G, Zangrillo A; Italian ECMOnet., Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score., 2013, PMID:23160769
- Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C, Brochard L; REVA Research Network., Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis., PMID:23155145
- Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC 2nd, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG Jr., Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study., 1979, PMID:490805
- Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, Harvey C, Cordingley JJ, Price S, Vuylsteke A, Jenkins DP, Noble DW, Bloomfield R, Walsh TS, Perkins GD,

Menon D, Taylor BL, Rowan KM., Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1)., 2011, PMID:21976615

- Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, Philipp A, Wernecke KD, Lubnow M, Slutsky AS., Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study., 2013, PMID:23306584
- Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, Trouillet JL, Bréchot N, Nieszkowska A, Dupont H, Ouattara A, Leprince P, Chastre J, Combes A., The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome., 2013, PMID:23907497
- Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Herrmann P, Mascia L, Quintel M, Slutsky AS, Gattinoni L, Ranieri VM., Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome., 2007, PMID:17038660
- Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM., Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal., 2009, PMID:19741487
- Madjdpour C, Jewell UR, Kneller S, Ziegler U, Schwendener R, Booy C, Kläusli L, Pasch T, Schimmer RC, Beck-Schimmer B., Decreased alveolar oxygen induces lung inflammation., 2003, PMID:12388372
- Bellani G, Guerra L, Musch G, Zanella A, Patroniti N, Mauri T, Messa C, Pesenti A., Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury., 2011, PMID:21257791
- Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S; Emergency Medicine Shock Research Network (EMShockNet) Investigators., Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality., 2010, PMID:20516417
- Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, Localio AR, Demissie E, Hopkins RO, Angus DC., The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury., 2012, PMID:22492988
- Del Sorbo L, Cypel M, Fan E., Extracorporeal life support for adults with severe acute respiratory failure., 2014, PMID:24503270

5. 1. Indications and Rationale

ECMO facilitates oxygenation and ventilation via an oxygenating shunt as opposed to relying on the ventilator to use the non-compliant, injured lung beyond lung protective limits in an attempt to achieve adequate oxygenation and ventilation. This strategy of off-loading the lungs helps facilitate “lung rest and recovery” and minimises ventilator-associated lung injury (VALI).

VALI is characterised by volutrauma and barotrauma (volume and pressure overload leading to over distension), atelectrauma (cyclic recruitment and derecruitment) and biotrauma (lung inflammation that develops as a consequence of the mechanical forces above). Strategies to protect against VALI include minimising tidal volumes to 6 mL/kg PBW and plateau pressures to <30 cmH_2O. Despite strict adherence to optimal lung protective ventilation, some patients with severe ARDS may still experience tidal hyperinflation, VALI and develop life threatening progressive hypoxia and hypercapnia. ECMO provides sufficient stability with gas exchange to facilitate lung protection or even “ultra” lung protective mechanical ventilation.

ECMO provides an ideal environment to facilitate lung protective or even “ultra”-lung protective ventilation by offloading the lungs, in part, through an oxygenating and ventilating shunt.

5. 2. Veno-Venous ECMO For ARDS

Veno-venous ECMO is the most common configuration for severe hypoxaemia and hypercapnia in patients with ARDS:

- Femoral (drainage) - internal jugular (return)
- Bicaval dual lumen cannula (superior and inferior vena cava drainage and right atrium return)
- Femoral (drainage) - contralateral femoral (return)

In the presence of cardiogenic shock, veno-arterial (VA) or veno-veno-arterial (VA-V) ECMO are the modalities of choice.

Highly oxygenated blood delivered to the pulmonary circulation from the ECMO circuit reverses hypoxemic pulmonary vasoconstriction, increasing perfusion to poorly ventilated lung units. At the initiation of ECMO, the contribution of the native lungs to systemic gas exchange may be minimal. With some improvement in native lung function, lower ECMO blood flow rates can be tolerated, so that a greater proportion of blood flowing through the pulmonary artery is poorly oxygenated, potentially allowing improved V/Q matching and a greater contribution of native lungs to systemic oxygenation.

During the early phase of ECMO for ARDS, a high ECMO blood flow is required to maintain oxygenation, and as the native lungs recover, a lower ECMO blood flow rate can be tolerated. When initiating ECMO in a hypoxic but severely hypercapnic patient, a low sweep gas flow is used to prevent too rapid a correction of pH and $PaCO_2$ by the highly efficient ECMO gas exchange device.

5. 3. ECCOR For ARDS

An alternative indication for ECLS in the setting of ARDS is to facilitate “ultra” lung protective ventilation using an $ECCO_2R$ device. In patients with satisfactory oxygenation but severe hypercapnia, ECCO2R may allow tidal volumes of 3-4 mls/kg predicted body weight and plateau pressures of <25 cmH_2O to be used.

$ECCO_2R$ may be useful when a patient with ARDS has severely non-compliant lungs that prevent the delivery of lung protective ventilation (i.e., tidal volumes of 6 mL/kg PBW or plateau pressures <30 cmH_2O), or as a rescue from injurious levels of mechanical ventilation. Hypothetically, ECCO2R may allow an “ultra”-lung protective ventilatory strategy to be used aiming for tidal volumes of 3-4 cc/kg and plateau pressures of <25 cmH_2O.

5. 4. Configurations of ECLS for ARDS

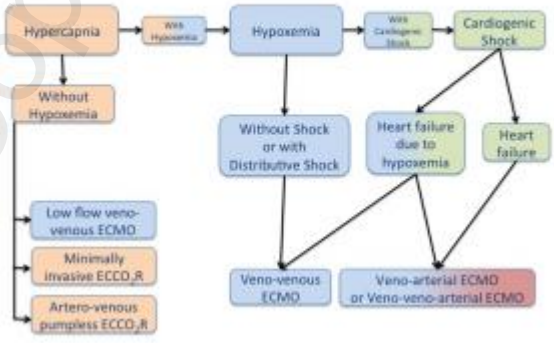

Figure 15: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti

A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

5. 5. Clinical Evidence

There has been significant improvement in survival rates associated with ECLS use in patients with ARDS, with the earliest trials in the 1970's demonstrating extremely poor survival rates (10%) to survival rates exceeding 70% in some recent publications.

Earlier trials were characterised by the continued use of injurious ventilation, use of the veno-arterial (VA) rather than VV ECMO, late initiation of ECMO, high dose anticoagulation and high transfusion requirements.

Advancements in ECLS circuit technology, improved knowledge of ventilator-associated lung injury, less intensive anti-coagulation and earlier initiation of ECLS have contributed to more favourable outcomes over the past two decades, renewing enthusiasm for the role of ECLS for severe ARDS.

A randomised controlled trial from the United Kingdom in 2009 randomised patients with severe ARDS to transfer to a specialist centre for consideration of ECMO as compared to continued conventional therapy in the referral hospital. The patients transferred for consideration of ECMO had a significant reduction in 6-month mortality without disability (RR 0.69; 95% CI 0.05-0.97, p = 0.03).

However, only 76% of patients randomised for consideration of ECMO actually received ECMO. The other important consideration is that only 70% of the control arm patients (compared to 93% of the intervention arm) received lung protective ventilation. Thus, the survival benefit conferred was more likely related to being at a "centre of excellence" where ECMO might have been part of the management strategy as opposed to the direct benefit of ECMO alone. The following table outlines studies over the years for ECMO in ARDS

Evidence:

Table 4: Pivotal Studies of ECMO for ARDS

	Indication	Modality	Outcome	Shortcoming
ZAPOL, 19794	SEVERE ARDS	VA ECMO	HIGH MORTALITY <10% survival rates in ECMO and conventional groups	Out dated technology Significant bleeding VA configuration Late initiation (>7 days)
PEEK, 20091 (CESAR TRIAL)	SEVERE ARDS	VV ECMO	63% survival of ECMO arm compared to 47% conventional ventilation (statistically significant)	More compliance with lung protective ventilation in ECMO arm and only 76% of ECMO transfers received ECMO
NOAH, 20105	SEVERE ARDS, H1N1	VV ECMO	73% survival of ECMO arm compared to conventional ventilation (statistically significant - results robust across 3 different types of matching: Propensity score matching, individual matching, Genmatching)	Similar survival rates noted at centers and registries of H1N1 patients without ECMO use
PHAM, 20123	SEVERE ARDS, H1N1	VV ECMO	64% survival of ECMO arm not statistically better than conventional ventilation using REVA match	Matching technique so rigorous that patient population who derived MOST benefit from ECMO were excluded because no matches found (young, most severe ARDS)

5. 6. Evidence: ECCOR

Bein et al, recently published the first randomised controlled trial evaluating the impact of an “ultra”-lung protective strategy (using 3 mL/kg PBW tidal volumes) facilitated by $ECCO_2R$ for ARDS.

The primary endpoint was ventilator-free days at 28 days. While the overall population did not demonstrate a statistically significant increase in ventilator-free days, a post hoc analysis of patients in the more severe ARDS subgroup (PaO_2/FiO_2 <150 mmHg) demonstrated a significant improvement in ventilator free days. A larger trial is pending to further explore this association.

5. 7. Future Research:

While a strong physiological rationale for employing ECLS may exist, current research does not support its routine application for severe ARDS.

A multi-centre, international randomised controlled trial is currently underway to evaluate the clinical efficacy of VV-ECMO for ARDS. The Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (ClinicalTrials.gov NCT01470703) is evaluating the early initiation of VV ECMO for severe ARDS combined with a lung rest strategy as compared to a standardised lung protective ventilation control group.

Risk factors associated with a poor prognosis and increased mortality in ARDS patients treated with ECMO have been evaluated in different cohorts. More research is needed to further validate these variables.

Two studies, listed below, based upon observational data, have identified the following variables associated with a poor prognosis:

Table 5: Risk Factors Associated with Poor Prognosis in ARDS patients treated with ECLS

PRESERVE	**ECMO NET SCORE (H1N1)**
Immunocompromised Older age (>55 years old) High Sequential Organ Failure Assessment Score (>12) Duration of mechanical ventilation (>7 days) No prone positioning pre-ECMO PEEP <10 cmH_2O Plateau pressures >30 cmH_2O BMI >30 (protective)	Hospital length of stay prior to ECLS Total bilirubin Creatinine Hematocrit Mean arterial pressure

5. 8. Clinical Management and Controversies

Mechanical Ventilation

Optimal or 'rest' mechanical ventilation settings while on ECLS is an area of much debate. Most agree on a strategy of maximising the support provided by the ECLS circuit at the outset with a gradual transition to greater dependence upon mechanical ventilation once native lung recovery is evident.

Tidal Volume

Some patients with severe ARDS may experience tidal hyperinflation despite using a lung protective strategy, including 6 mL/kg predicted body weight (PBW). Perhaps in severe ARDS, 6 mL/kg PBW may not be sufficiently conservative to protect the "baby lung" and lower tidal volumes are needed. How low the tidal volume should be is not clear and there are currently no data to support a particular tidal volume or strategy, although 2 proof-of-concept studies have safely lowered tidal volume to 3-4 mL/kg PBW.

Plateau Pressures

Higher plateau pressures during ventilation with ARDS have been associated with a worse outcome. Extrapolating from this, lowering plateau pressure while on ECLS may lead to improved outcomes.

Positive End Expiratory Pressure (PEEP):

The optimal level of PEEP during ECLS is also unclear. Some would argue that PEEP related alveolar recruitment is no longer necessary given the oxygenation from ECMO. However, opening lung units and preventing atelectasis may have an impact on alveolar healing. Others investigators have demonstrated that when previously atelectatic lung units are opened, it may lead to an increased metabolic activity in those lung units and a release of inflammatory mediators.

Oxygen Thresholds

It remains unclear what the optimal PaO_2 threshold should be while on ECMO. While somewhat controversial, recent evidence post cardiac arrest suggests a possible deleterious impact of hyperoxia post arrest presumably due to ischemia-reperfusion and the presence of oxygen free radicals. On the contrary, a post hoc analysis of the ARDSNet trial demonstrated a higher incidence of neurocognitive impairment in the subgroup with a lower PaO_2 threshold. Given the uncertainty of the risk of hyperoxia and the suggestion of harm with severe hypoxemia, we recommend targeting modest oxygenation targets similar to those from ARDSnet (i.e., SpO_2 88-93%) until further evidence is available.

Carbon Dioxide Thresholds

It is unclear whether permissive hypercapnia should be tolerated or targeted in ARDS patients. While we know that permissive hypercapnia can be safely tolerated, CO_2 removal with ECMO may lead to rapid normocapnia in patients with ARDS. We recommend targeting modest pH goals similar to those from the ARDSnet trial (i.e., pH 7.25-7.45) until further evidence is available.

Weaning

When evidence of clinical improvement occurs (e.g., improved respiratory mechanics, tidal volumes on similar ventilator settings, gas exchange), this may be an indication that the patient is ready to be weaned from ECMO.

VV ECMO is weaned primarily by reducing sweep gas flow while maintaining ECMO blood flow and anti-coagulation. Mechanical ventilation settings should be increased to compensate for lower ECMO support. Once the patient can tolerate zero sweep gas flow with modest mechanical ventilator settings (e.g. tidal volume < 6 ml/kg of predicted body weight, plateau pressure < 30 cmH2O, PEEP < 12 cmH_2O, FiO_2 < 0.6), decannulation should be considered.

Anticoagulation Management

Most modern ECLS circuits are heparin coated and engineered with biocompatible materials leading. This leads to a lower requirements for systemic heparin anticoagulation as well as less haemolysis and platelet consumption by the circuit.

Despite these advancements; however, systemic anticoagulation is still required, most often in the form of unfractionated heparin. Factors that impact anticoagulation targets depends upon three major factors: ECLS technique (VA vs. VV vs. $ECCO_2R$), blood flow rate (lower flows higher risk of thrombus formation), and the presence of bleeding.

Typical anticoagulation targets include: Activated clotting time (ACT) 1.5 times normal, activated partial thromboplastin time (aPTT) 1.2-2.8 times normal, anti-Xa activity 0.2-0.3 IU/ml,. Thromboelastography may also be considered.

If heparin requirements are noted to increase substantially on ECLS (e.g., > 50 units/kg/hr), screening for anti-thrombin deficiency may be.

Blood Transfusion Thresholds

Optimal transfusion thresholds have not be rigorously evaluated for patients on ECMO. While the Extracorporeal Life Support Organization suggest targeting normal values of haemoglobin (>10g/dl) in attempt to optimize tissue oxygen delivery, some centres target a more conservative threshold of 7 g/dl, given the risks associated with transfusions. More research is needed to understand what the optimal haemoglobin threshold is while on ECMO.

6. ECLS for Obstructive Lung Diseases

References found in this Chapter

(Abrams and Brodie. 2013; O'Donnell and Parker. 2006; Laghi and Goyal. 2012; McFadden ER 2003; Braune and Kluge 2013)

References

- Abrams D, Brodie D., Emerging indications for extracorporeal membrane oxygenation in adults with respiratory failure., 2013, PMID:23952860
- O'Donnell DE, Parker CM., COPD exacerbations . 3: Pathophysiology., 2006, PMID:16565268
- Laghi F, Goyal A. , Auto-PEEP in respiratory failure., 2012, https://pdfs.semanticscholar.org/8830/3b679e1d7cfdb85ec951cef4f8f6b35ee7af.pdf
- McFadden ER Jr, Acute severe asthma., 2003, PMID:14522812
- Braune SA, Kluge S, Extracorporeal lung support in patients with chronic obstructive pulmonary disease., 2013, PMID:23698548

6. 1. Rationale and Evidence

The main pathophysiological characteristic of obstructive lung disease exacerbation is the expiratory flow limitation caused by the increased resistance of the small airways. The development of dynamic alveolar hyperinflation and intrinsic PEEP increase the work of breathing in these patients, leading to respiratory muscle fatigue and rapid shallow breathing. The reduction of alveolar ventilation and rise in $PaCO_2$ further increases the ventilatory demand, creating a vicious loop.

In this setting, non-invasive ventilation (NIV) reduces the work of breathing and increases alveolar ventilation, but may not be sufficient in severe cases. Invasive mechanical ventilation (IMV) can normalise gas exchange and reduce the work of breathing, but is associated with adverse effects, such as ventilator-associated pneumonia, ICU-acquired weakness, and ventilator-induced diaphragmatic dysfunction.

$ECCO_2R$ reduces the volume of alveolar ventilation required to eliminate CO_2 production. The consequent reduction of tidal volume and respiratory rate is associated with increased expiratory time, facilitating the resolution of the dynamic hyperinflation. Therefore, the work of breathing decreases despite persistent airflow limitation.

Given this strong pathophysiological rationale, the application of $ECCO_2R$, has been described in several case reports of patients with obstructive lung diseases. However, until there are randomised trials providing definitive proof of its efficacy, we cannot recommend the routine use of $ECCO_2R$ in these patients.

6. 2. Configurations

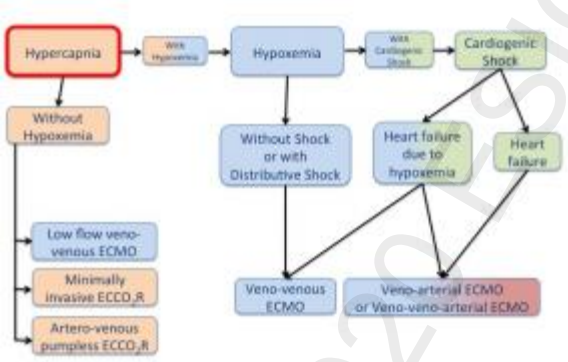

Figure 16: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

6. 3. Indications and Goals Reported in the Literature

Potential Indications:

1. Invasive mechanical ventilation for COPD exacerbation with failed two or more weaning attempts
2. Failing treatment with NIV:
    1. NIV for at least 1 -2 hours with signs of respiratory distress (i.e., respiratory rate ≥30 breaths/min and use of accessory muscles or paradoxical abdominal movements), and

2. $PaCO_2$ > 55 mmHg and pH < 7.25, or
3. pH < 7.30 and $PaCO_2$ > 55 mm Hg, with $PaCO_2$ decrease < 5 mmHg from baseline

Clinical goals:

- Prevention of endotracheal intubation
- Facilitation of weaning from invasive mechanical ventilation
- Early mobilisation and physiotherapy

7. ECLS for COPD Exacerbation

Table 6: Selected Case Series of ECLS for COPD Exacerbations

	Modality	No. of treated patients and outcome	Complications	Reference
Pesenti A, 1990 First description of ECLS for COPD exacerbation	$ECCO_2R$ and IMV	1 patient, survived	None	Anesthesiology 1990;72:571-3
Abrams DC, 2013 ECLS to facilitate weaning from IMV	$ECCO_2R$ and IMV	5 patients; age 73 ± 8.7 years All weaned from IMV Duration of IMV post $ECCO_2R$: 4 hours (1.5–21.5) Duration of $ECCO_2R$: 193.0 ± 76.5 hours Time to ambulation after $ECCO_2R$ initiation: 29.4 ± 12.6 hours	Minor bleeding in 2/5 patients	Ann Am Thorac Soc. 2013;10:307-14

Kluge S, 2012 ECLS during NIV to prevent IMV	Pumpless arterio-venous ECCO2R and NIV	21 patients with hypercapnia, 14 with COPD age 58 (27-80) years Gas exchange parameters before ECLS: pH 7.28 (7.10–7.41) $PaCO_2$ 84.0 (54.2–131.0) mmHg PaO_2/FiO_2 ratio 208 (153–396) Duration of $ECCO_2R$: 9 (1–116) days Intubation: 10% -28-day mortality: 24%	9 patients with bleeding 1 patient with pseudo aneurism of femoral artery 1 patient with heparin-induced thrombocytopenia	Intensive Care Med 2012;38:1632-9
Burki NK, 2013 ECLS during NIV to prevent IMV, and during IMV to facilitate weaning	ECCO2R	20 patients with COPD: 9 on NIV, 11 on IMV age 49-78 years Duration of $ECCO_2R$: 0.2-192 hours none of the patients on NIV was intubated 3/11 patients on IMV were successfully weaned	3 patients with bleeding 1 patient with catheter related deep vein thrombosis 1 patient with catheter related pneumothorax 1 patient with lethal catheter related iliac vein perforation	Chest 2013;143:678-86.

- IMV = Invasive Mechanical Ventilation

8. ECLS for Near Fatal Asthma Exacerbation

8. 1. Indications and Configurations

Severe dynamic lung hyperinflation with consequent refractory hypercapnia characterise near fatal episodes of asthma exacerbation.

ECLS has been used as rescue strategy in these patients as an adjunct to mechanical ventilation. ECLS can correct gas exchange, thereby prolonging the duration of the expiratory time and thus facilitating the reduction of dynamic lung hyperinflation, while providing time for the resolution of bronchospasm.

Low flow $ECCO_2R$, by correcting respiratory acidosis, may accomplish the goal of facilitating the resolution of dynamic lung hyperinflation. However, the most severe cases of asthma exacerbation can be characterised by hypoxemia and hemodynamic decompensation. In these conditions, VV-ECMO or VA-ECMO provides a more adequate means of support, especially in case of rescue conditions.

8. 2. Evidence

Table 7: Selected Case Series of ECLS for Near Fatal Asthma

	Modality	No. of treated patients and outcome	Complications	Reference
MacDonnell KF, 1981 First description of ECLS for asthma	ECMO and IMV	1 patient, survived	None reported	Ann Thorac Surg. 1981;31(2):171-5

Hebbar KB, 2009 ELSO report on ECLS for severe refractory status asthmaticus in children	VV-ECMO or VA-ECMO and IMV	1896-2007 64 patients; age 10 years (1-17) Gas exchange parameters with IMV before ECLS: pH 6.96 (6.78 - 7.28) $PaCO_2$ 123 mmHg (70 – 237) PaO_2 126 mmHg (59 – 636) Duration of ECLS: 94 hours Survival rate 94%	Neurologic 6% Cardiovascular 33% Bleeding 23% Mechanical 23% Pulmonary 14% Metabolic 31% Renal 18% Infectious 16%	Crit Care. 2009;13(2):R29
Mikkelsen ME, 2009 ELSO report on ECLS for severe refractory status asthmaticus in adults	VV-ECMO or VA-ECMO and IMV	1986-2006 24 patients; age 31.3 ± 12.3 years Gas exchange parameters with IMV before ECLS: pH 7.17 ± 0.16 $PaCO_2$ 119.7 ± 58.1 mmHg PaO_2/FiO_2 ratio 244 ± 180 Duration of ECLS: 111.9 ± 71.2 hours Survival rate 83.3%	In 79.2% of patients Bleeding 37.5% Cardiovascular 33.3% Infection 8.3% Mechanical 41.6% Neurologic 12.5% Renal failure 12.5%	ASAIO J. 2009;55(1):47-52
Brenner K, 2014	$ECCO_2R$ and IMV	2 patients, both survived	None reported	Perfusion. 2014;29(1):26-8

- IMV = Invasive Mechanical Ventilation

9. ECLS as a bridge to lung transplant

References found in this Chapter

(Cypel and Keshavjee. 2011; Strueber 2011; Diaz-Guzman, Hoopes and Zwischenberger. 2013; Toyoda et al. 2013; Bittner et al. 2012)

References

- Cypel M, Keshavjee S., Extracorporeal life support as a bridge to lung transplantation., 2011, PMID:21511087
- Strueber M, Bridges to lung transplantation., 2011, PMID:21897243
- Diaz-Guzman E, Hoopes CW, Zwischenberger JB., The evolution of extracorporeal life support as a bridge to lung transplantation., 2013, PMID:23271390
- Toyoda Y, Bhama JK, Shigemura N, Zaldonis D, Pilewski J, Crespo M, Bermudez C., Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation., 2013, PMID:23332185
- Bittner HB, Lehmann S, Rastan A, Garbade J, Binner C, Mohr FW, Barten MJ., Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery., 2012, PMID:22748640

9. 1. Definition

“Bridge to lung transplant” defines strategies to utilise artificial support to manage the acute decompensation of patients with chronic respiratory failure awaiting a suitable organ. Clinical advancements in this field are particularly required, as the mortality rate of patients on the lung transplant waiting list is still very high (14.1% in North America in 2009) and higher than those of other solid organs transplant.

The goal of bridge strategies to lung transplant should be preferably to improve the critical condition of patients with end stage respiratory failure, preventing multi-organ dysfunction and restoring physiological homeostasis in order to increase the chances of a successful transplant. Ideally, bridge to lung transplant should not be applied with the sole intent of prolonging the pre-transplant life expectancy of patients. This approach, in fact, would raise ethical issues by potentially selecting for transplantation very ill patients for lung transplantation with long-term outcomes that are likely to be poor.

9. 2. Rationale and Evidence

Invasive mechanical ventilation (IMV) may be considered a bridging strategy to lung transplantation as it improves gas exchange and decreases the work of breathing, but it is associated with several injurious side effects. Indeed, patients with end stage lung diseases are particularly susceptible to ventilator-associated lung injury and pneumonia. Moreover, the application of IMV often requires patients to be sedated and bed-bound, reducing their ability to undergo adequate physiotherapy. These events lead to severe deconditioning of these critically ill patients and may compromise their suitability for transplant.

The increased efficiency of the ECLS systems in maintaining adequate gas exchange with fewer complications has resulted in the possibility to remarkably reduce the need for IMV.

The use of a single, bi-caval dual-lumen cannula in the internal jugular vein for ECLS represents an important technological advancement for these patients. By accessing only one vessel, preferably in the upper body, it becomes possible to deliver more intensive physical therapy and rehabilitation in the pre-transplant period while on ECLS. This innovative strategy may result in shorter duration of post-transplant mechanical ventilation and hospital stay, with less morbidity and mortality.

9. 3. Indications

There are no evidence-based Indications and contraindications to ECLS as a bridge to transplant, but there is general consensus that young age, absence of multiple-organ dysfunction and good potential for rehabilitation are criteria for ECLS as a bridge to transplant. Septic shock, multi-organ dysfunction, severe arterial occlusive disease, heparin-induced thrombocytopenia, long duration of mechanical ventilation, and advanced age are considered at least relative contraindications. The appropriate selection of patients and ECLS mode and configuration has been crucial in obtaining progressively better outcomes.

Several recent case series and observational studies have shown that the post-transplant mortality rate of selected patients bridged to transplant with ECLS is comparable to that of patients transplanted without pre-transplant ECLS.

Despite these promising results, the application of ECLS as a bridge to transplant remains controversial and better quality data on its putative risks and benefits are needed before routine adoption in clinical practice can take place.

9. 4. Configurations

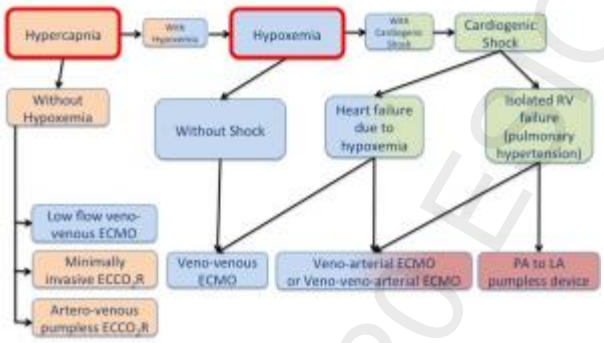

Figure 16: Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Fan E, Gattinoni L, Combes A, Schmidt M, Peek G, Brodie D, Muller T, Morelli A, Ranieri VM, Pesenti A, Brochard L, Hodgson C, Van Kiersbilck C, Roch A, Quintel M, Papazian L. Intensive Care Med. 2016 May;42(5):712-724. doi: 10.1007/s00134-016-4314-7. Epub 2016 Mar 23. Illustration by Alberto Goffi

9. 5. Evidence

Table 8: Selected Case Series of ECLS as a Bridge to Lung Transplant

	Modality	No. of treated patients and outcome	Reference

Veith FJ, 1977	First successful ECLS as bridge to lung transplant	ECMO and IMV1 patient survived pre-transplant died post transplant	Transplant Proc. 1977;9(1):203-8
Bermudez CA, 2011	VV or VA-ECMO and IMV	17 patients with COPD, idiopathic pulmonary fibrosis, cystic fibrosis, graft failure; age: 40 ± 14 year Duration of ECLS: 1-49 days Mortality rate pre transplant: 0% Survival rate: 74% at 1 year	Ann Thorac Surg. 2011;92:1226-32
De Perrot M, 2011	VA-ECMO or Pumpless pulmonary artery-left atrium circuit	6 patients with idiopathic pulmonary hypertension Duration of ECLS: 1-69 days 4 patients required IMV Mortality rate pre transplant: 0% Survival rate post transplant: 66%	J Heart Lung Transplant. 2011;30:997-1002
Fuehner T, 2012	Awake ECMO	26 patients with pulmonary fibrosis, cystic fibrosis, graft failure, pulmonary hypertension; age: 44 (23-62) years 7 patients required IMV Duration of ECLS: 9 (1-45) days Mortality rate pre transplant: 23% Survival rate post transplant: 80% at 6 months	Am J Respir Crit Care Med.2012;185:763-8
Lafarge M, 2013	VV or VA-ECMO	36 patients with pulmonary fibrosis (20), cystic fibrosis (11), others (5); age: 30.8 (22.4–47.7) years 33 patients with IMV before ECLS Duration of ECLS pre transplant: 3.5 (0-11) days Mortality rate pre transplant: 16.7% Survival rate post transplant: 47% at 17 months	J Heart Lung Transplant 2013;32:905–913

- IMV = Invasive Mechanical Ventilation

10. Complications and Troubleshooting

Table 9: Complications Associated with ECLS

CIRCUIT/OXYGENATOR	CANNULA	ANTICOAGULATION	PATIEN
Air In Circuit	Limb ischemia	Bleeding	Line Seps
Minor Air: Release air from oxygenator and look for cause (cracked line, air entranced through other venous access) **Major Air:** (sufficient quantity to cause pump to fail or on arterial side), may need to clamp and change circuit, look for cause (cracked or displaced line)	May occur with femoral arterial cannula obstructing distal flow to limb. Can address by adding a distal perfusion catheter, increasing flows, or decreasing vasopressors	Identify whether the bleeding is related to surgical procedure (post operative patient) or degree of anticoagulation. May benefit from decreasing anticoagulation threshold, stopping anticoagulation temporarily or anti-fibrinolytic/clotting agents (tranexamic acid/recombinant factor VIIa depending upon severity) or surgical/procedural exploration of the bleed depending upon source.	Use sterile technique for all central lin and ECM cannulatic sites. Avo any unnecessa central lin in order to minimize t risk of catheter related blood stream infections seeding th ECMO cannula
Clot or Thrombus Formation	Low flow or No Flow		Ventilator Associate Pneumoni

Identify cause (insufficient ECLS blood flow, insufficient anti-coagulation, platelet activation/aggregation, underlying hypercoagulable state ,i.e. heparin induced thrombocytopenia)	If no flow after insertion, assess for kinking, thrombus formation and depth of insertion		
Hemolysis	Deep Vein Thrombosis	Heparin-induced thrombocytopenia	Respirator Muscle Weakness
High flows inducing sheering of cells/hemolysis, look for alternative patient-associated causes of hemolysis (transfusion reaction etc). May benefit from decreasing flows. Less of a problem with contemporary ECLS equipment.	Large venous cannula could lead to the development of DVTs if the cannula is sufficiently large that it induces stasis proximal to its insertion. Ensure cannula size is not too big for vessel	Identify whether heparin induced thrombocytopenia is present, if confirmed, employ use of alternative anticoagulation agents (ie. Argatroban, bivaluridin)	Minimizati of sedatio and use o spontaneo mode of ventilation may reduc respiratory muscle weakness
Thrombocytopenia, platelet dysfunction	Vessel Dissection		Delirium

Platelets adhere to surface of circuit and become activated, platelet aggregation, consumption and further activation of coagulation system may result. May require platelet transfusions	Vessel dissection could be induced by insertion. Monitoring of distal perfusion is essential and if there is concern, consult vascular surgery		

Table 10: Troubleshooting Hypoxemia

ECMO RELATED STRATEGIES or ETIOLOGIES	
PATIENT RELATED ISSUES. Insufficient oxygen delivery?	Optimize cardiac preload, haemoglobin, inotropy. Evaluate the need to increase ECLS blood flow to achieve a target SaO_2 of 88-93%. If at maximal blood flow/cannula size, evaluate for a need to insert larger cannula to increase venous drainage (add an additional cannula) to provide more blood flow
Increase in oxygen consumption?	May need to increase blood flow to match oxygen consumption of patient (as above, optimize oxygen delivery through volume, haemoglobin, increase blood flow, larger cannula, additional cannula)May need to decrease oxygen consumption of patient (i.e., sedation, neuromuscular blockade)
CIRCUIT RELATED ISSUES. Recirculation	Tips of cannulae located too close to each other allowing oxygenated blood to be pulled back to the ECLS circuit as opposed to progressing into the pulmonary circulation; an increase in pre-oxygenator PO2 indicates increased recirculation; progressive RV failure will also lead to increase recirculation

Cannula	Misplacement/kinking (may manifest as chatter, drop in flow for same revolutions per minute)
Chatter	Negative pressure of venous drainage cannula pulling on vasculature can manifest as line chatter. May require fluid if volume deplete, drop in flow if flow is too high, or assessment of cannula migration into smaller vessel
Oxygenator compromise	Clotting or fibrin deposition affecting integrity of oxygenator
If native lungs were contributing to systemic oxygenation, need to evaluate cause for worsening hypoxaemia	Worsening underlying process/ARDS. Volume overload Transfusion associated lung injury Pulmonary embolism Anemia