Principle, management & monitoring of patients on ECMO
Role of ECMO & ECCO2 R in ARDS

Kodati Rakesh

HISTORY

ECLS (Extracorporeal life support)

- Encompasses all extracorporeal technologies and life support components including oxygenation, carbon dioxide removal, and haemodynamic support; renal and liver support may also be incorporated

- ECMO (VA & VV ECMO)
- ECPR
- ECCO2R

History

- 1971 – first successfully treated case of ARDS
- 1975 – first neonatal case
- 1978 – first description of ECCO2R
- 1989 – foundation of ESLO (Extracorporeal life support organisation)
- 2009 – renewed interest in ARDS (CESAR trial)
- 2009 – H1N1 pandemic, lead to widespread use

PROLONGED EXTRACORPOREAL OXYGENATION FOR ACUTE POST-TRAUMATIC RESPIRATORY FAILURE (SHOCK-LUNG SYNDROME)

Use of the Bramson Membrane Lung

First successful ECMO patient in1971

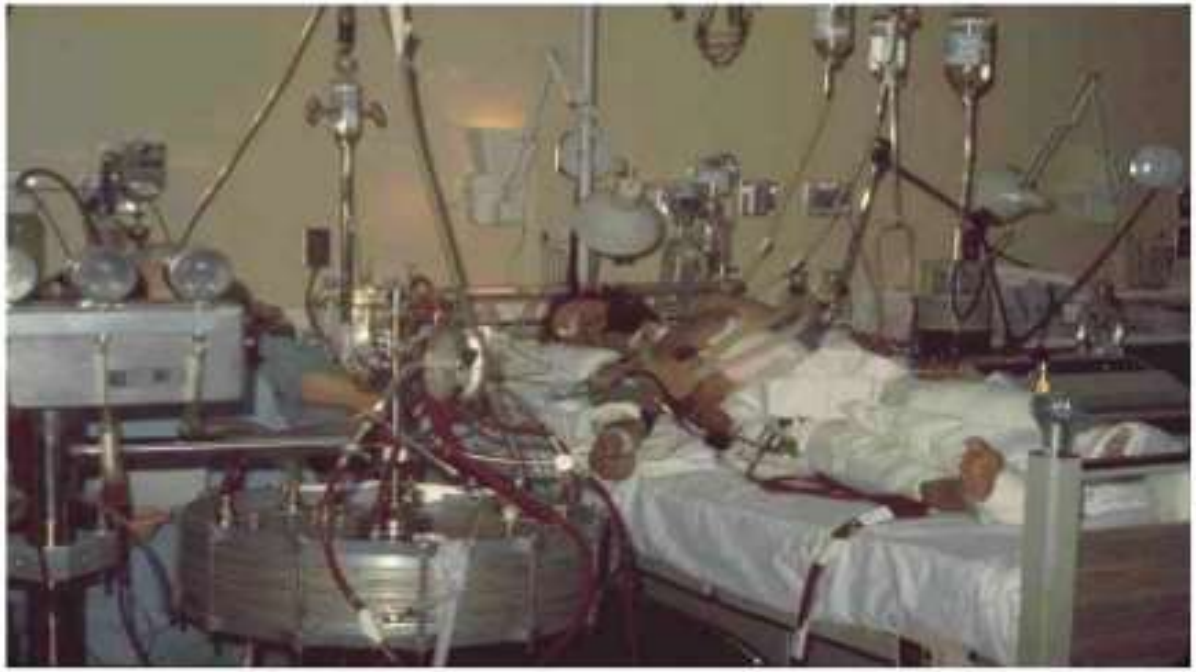


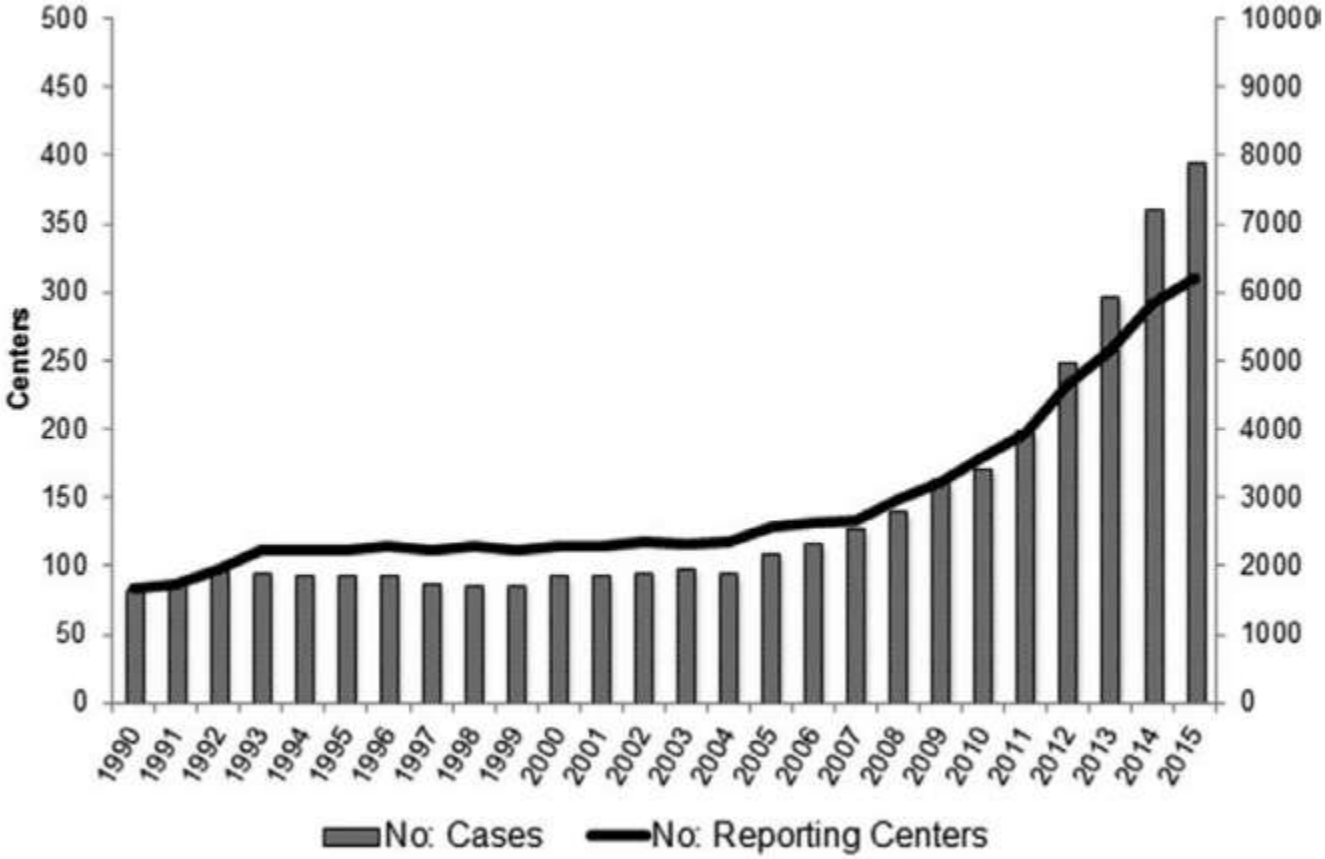
Figure 3.4. The first successful extracorporeal life support patient, treated by J. Donald Hill using the Bramson oxygenator (foreground), Santa Barbara, 1971.

ECLS registry report 2016

	No. Cases	Survived ECLS, N (%)	Discharged, N (%)
Neonatal			
Respiratory	29,153	24,488 (84)	21, 545 (74)
Cardiac	6,475	4,028 (62)	2,695 (42)
ECPR	1,336	859 (64)	547 (41)
Pediatric			
Respiratory	7,552	5,036 (67)	4,371 (58)
Cardiac	8,374	5,594 (67)	4,265 (51)
ECPR	2,996	1,645 (55)	1,232 (41)
Adult			
Respiratory	10,601	6,997 (66)	6,121 (58)
Cardiac	9.025	5,082 (56)	3,721 (41)
ECPR	2,885	1,137 (39)	848 (29)
Total	78,397	54,866 (70)	45,345 (58)

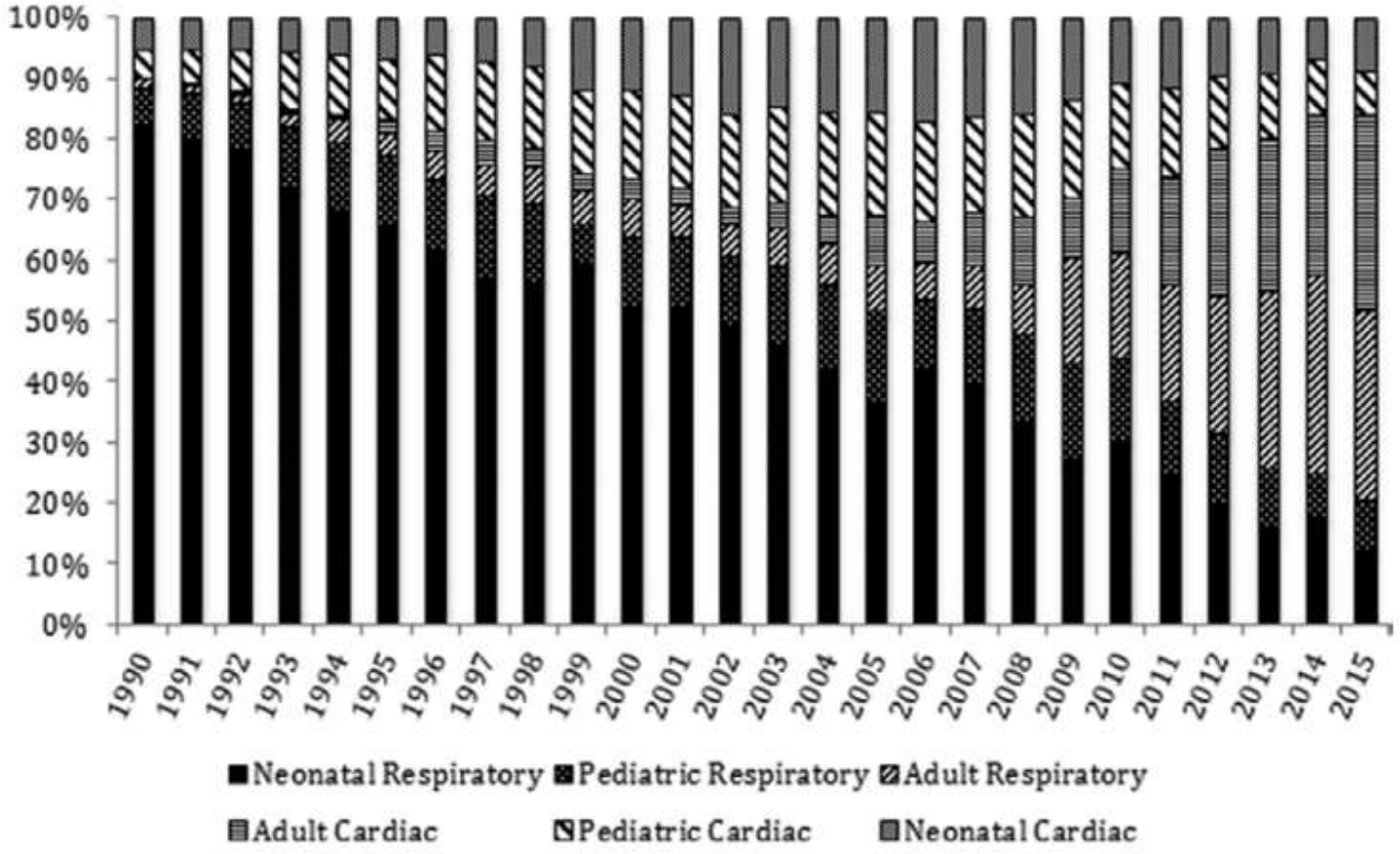
RR Thiagarajan et al, ELSO regitry, ASAIO Journal 2017

ECLS registry report 2016



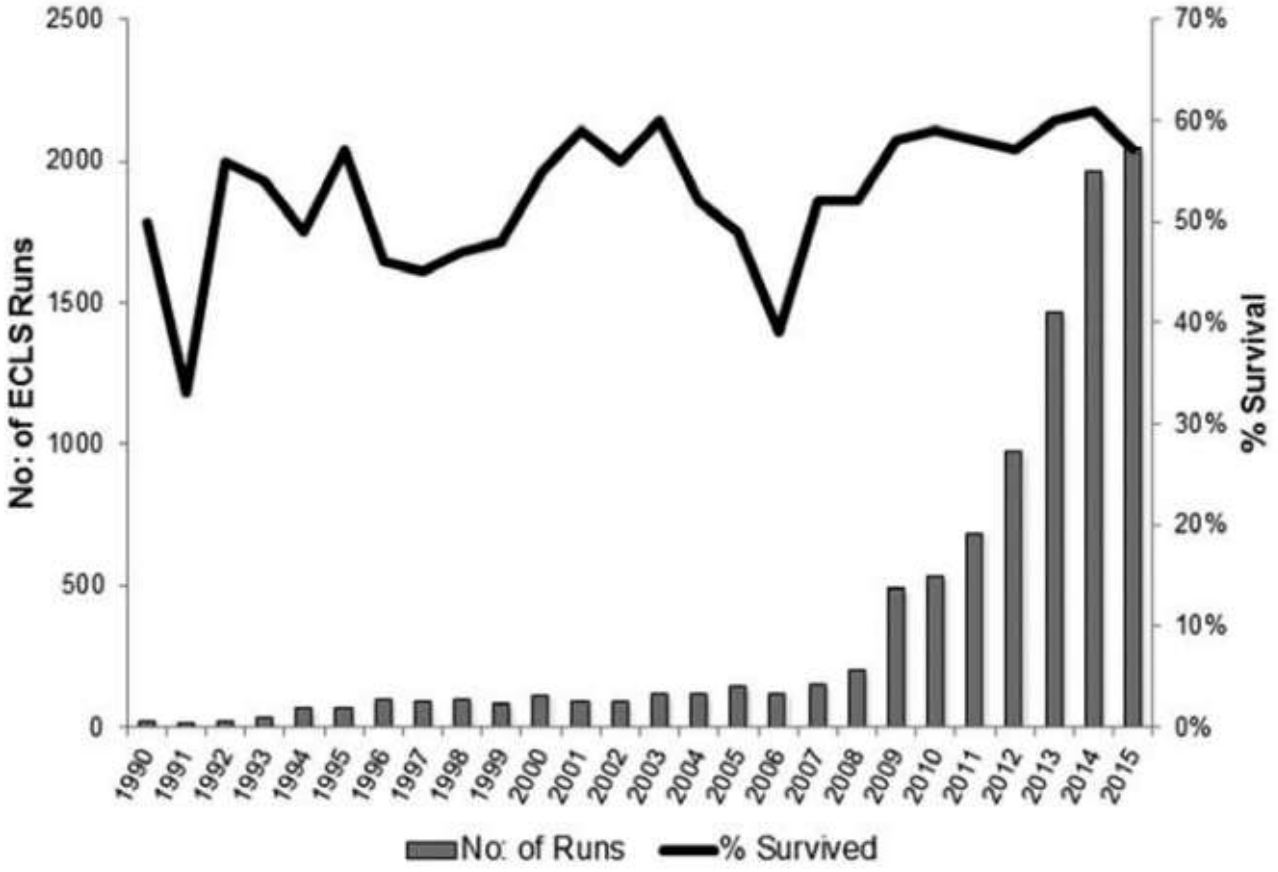
RR Thiagarajan et al, ELSO regitry, ASAIO Journal 2017

ECLS registry report 2016



RR Thiagarajan et al, ELSO regitry, ASAIO Journal 2017

ECLS in respiratory failure



RR Thiagarajan et al, ELSO regitry, ASAIO Journal 2017

BASIC PRINCIPLES

Principles

- To provide cardiopulmonary support in cases refractory to conventional management
- To correct gas exchange abnormalities not maintained by conventional support
- Used to prevent ventilator associated lung injury
  - Reducing the delivered volumes and airway pressures
  - Low FiO2 levels

Principles

- Bridging therapy, not a cure
  - Bridge to recovery – buying time for the patient to recover
  - Bridge to decision – temporary step till further decision
  - Bridge to transplant

Different from CPB..

CPB (cardiopulmonary bypass)	ECMO
Intraoperatively during cardiac sx	Intensive care units
Few hours	Longer duration of support
Low blood flow rates (2 l/min)	Higher flow rates (>4 l/min)
More anticoagulation	Less anticoagulation

Physiology - oxygenation

- Direct function of the blood flow
- Usual blood flow required is b/n 3 to 6 L/min
- Factors determining oxygenation
  - Thickness of the blood film
  - Fraction of inspired oxygen (FIO2)
  - Hemoglobin concentration
  - Oxygenation of the blood prior to membrane

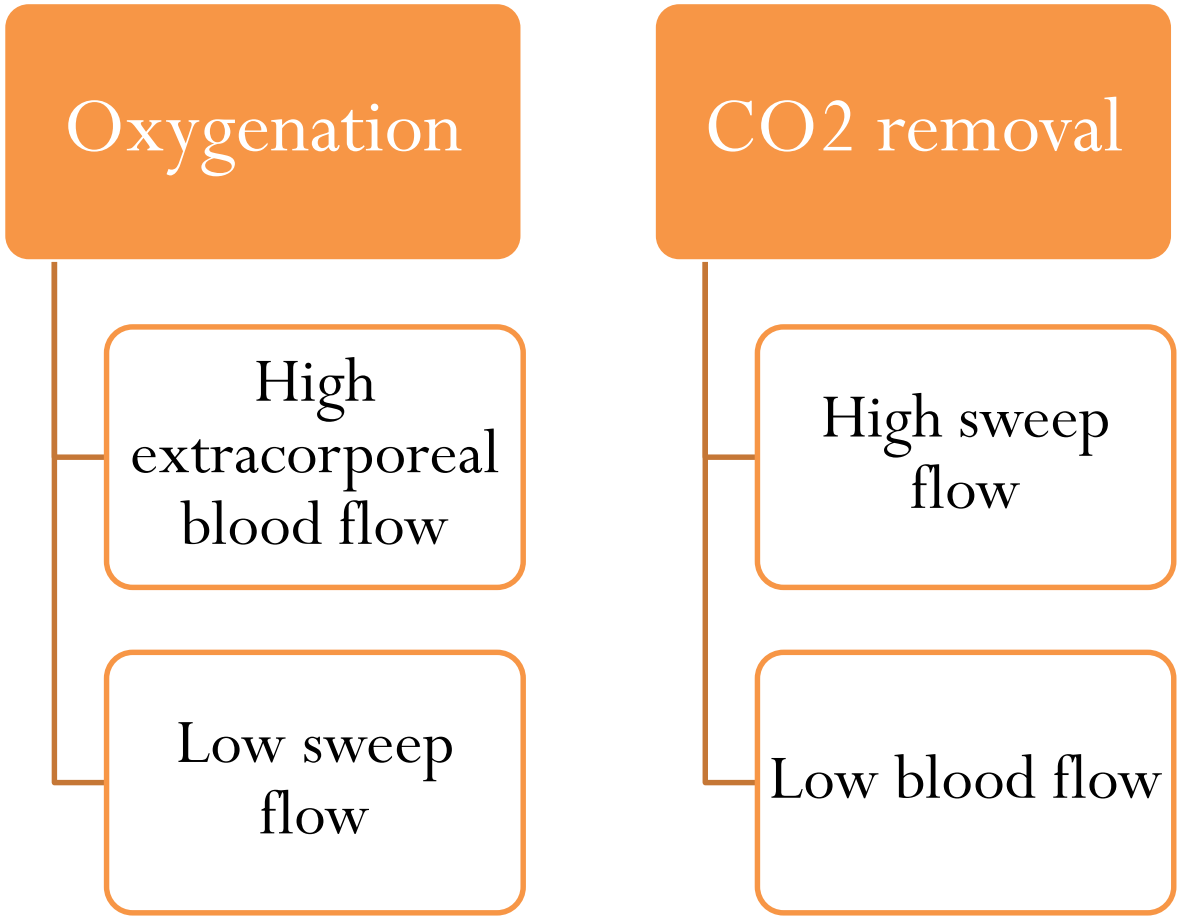
Gattinoni et al. Critical Care 2011, 15:243

Physiology – CO2 removal

- Direct function of "Sweep gas" flow rate
- Sweep flow – measure of gas flow across the membrane oxygenator
- CO2 exchange is much more efficient than O2 exchange
- May necessitate adding CO2 to the sweep gas to prevent excessive CO2 removal and respiratory alkalosis in neonates

Gattinoni et al. Critical Care 2011, 15:243

Physiology - Artificial lung



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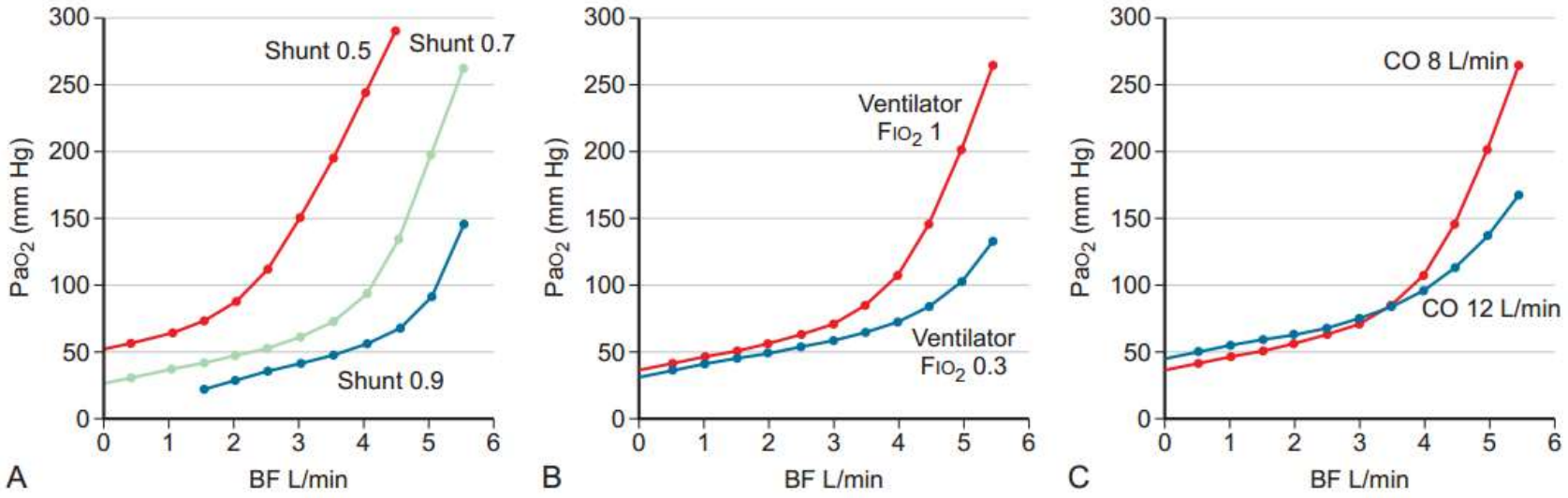
Physiology - Artificial lung



Murray Nadel Textbook of Respiratory Medicine, 6th Ed

Modes of access

- Veno - venous (V-V)
  - Isolated respiratory failure

- Veno - arterial (V-A)
  - Isolated cardiac failure
  - Cardiorespiratory failure

Venovenous ECMO

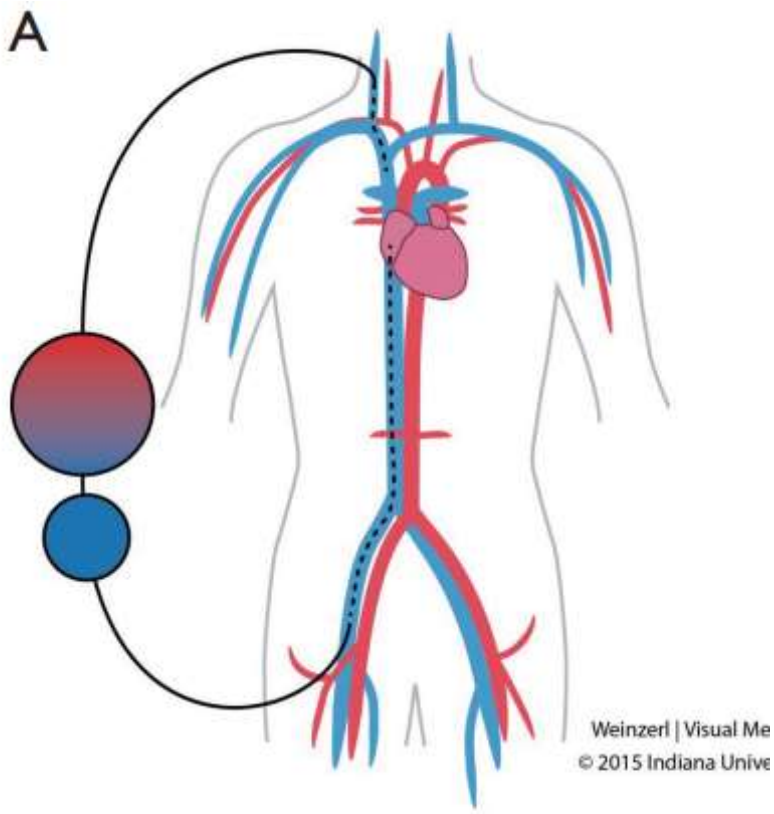
- Blood is extracted from the vena cava or right atrium and returned to the right atrium
- Provides respiratory support, but the patient is dependent upon his or her own hemodynamics
- Systemic blood flow and pressure are the result of the native cardiac function unrelated to the extracorporeal flow

Venovenous ECMO

- The PaO2 is determined by the mixing effect of oxygenated blood returning from the ECMO circuit to the right heart and deoxygenated blood returning from the bronchial admixture, coronary sinus, and vena cava

- Connected in series with lungs and heart

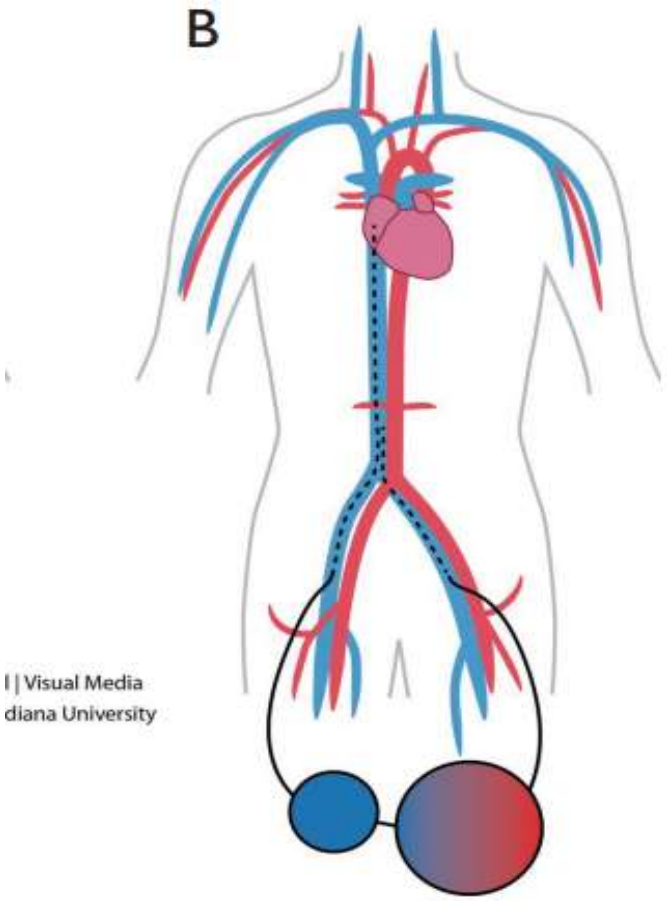
Venovenous ECMO



- Most frequently used
- Drainage though femoral venous cannula in IVC
- Infusion through IJV cannula proximal to RA

Femoral vein (drainage)
Jugular vein (infusion)

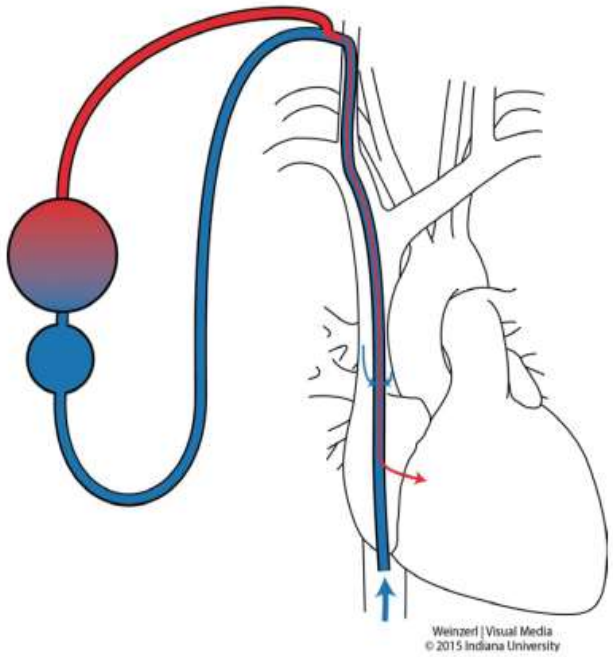
Venovenous ECMO



Femoral vein (drainage)
Femoral vein (infusion)

- Higher risk of recirculation
- Tip of the drainage cannula at the level of L1–L2, in order to receive the blood contribution of the renal veins
- Tip of the reimmission cannula should be placed close to the junction between the IVC & RA

Venovenous ECMO



Single cannulation with double lumen

- Cannula must cross the RA with the tip in the IVC
- Blood is drained from both the SVC & IVC
- Reinfusion occurs through a separate lumen into the RA just facing the tricuspid valve
- Early mobilisation & less need of sedatives

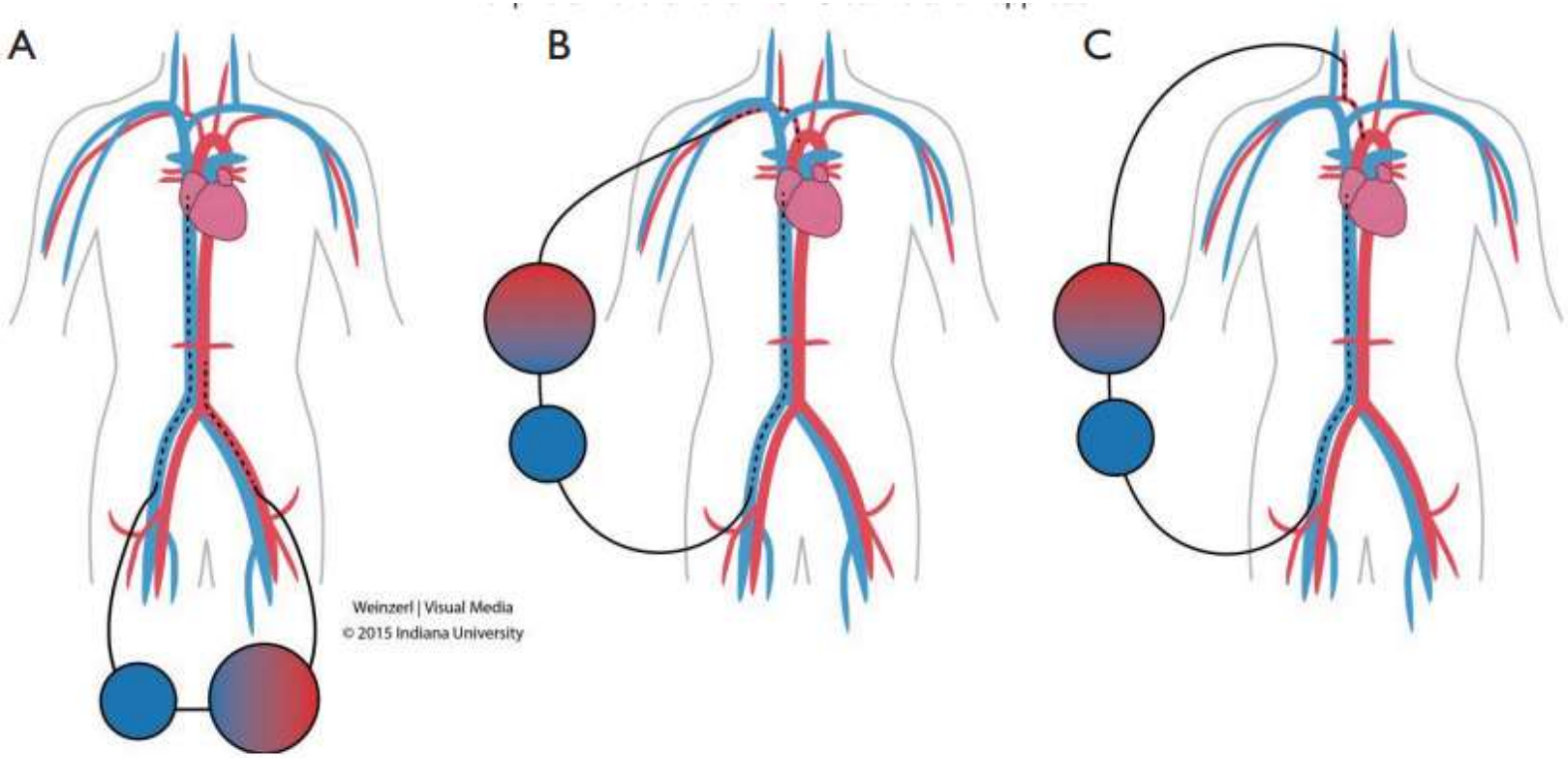
Venoarterial ECMO

- Blood is extracted from the right atrium or vena cava (for drainage), and returned to the arterial system either through peripheral cannulations via femoral, axillary or carotid arteries (for infusion)
- Connected in parallel with heart and lungs

Venoarterial ECMO

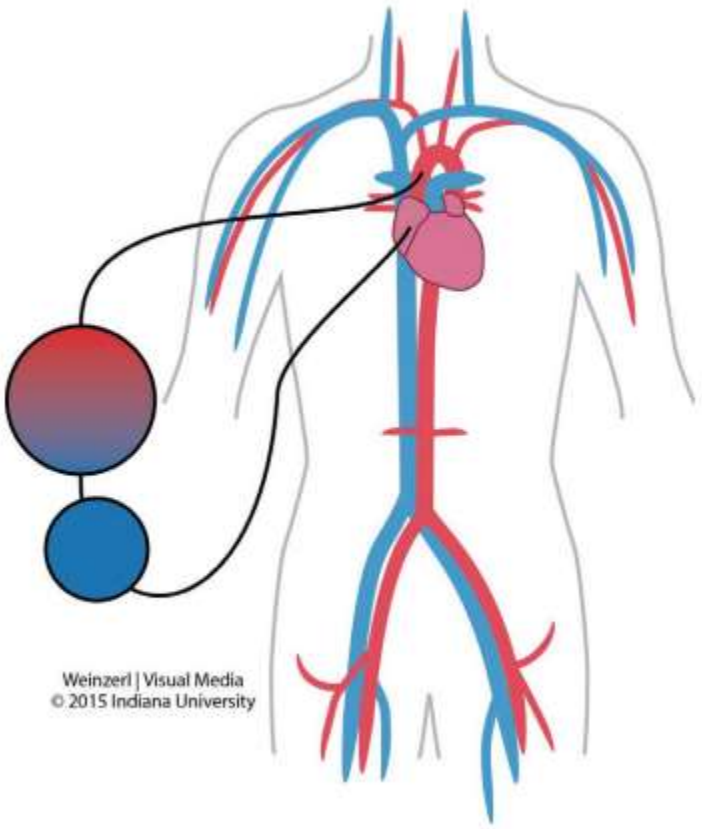
- Systemic flow, PO2 and CO2 levels are determined by combination of the blood added from the extracorporeal circuit plus the amount of blood passing through the native heart and lungs

Venoarterial ECMO



Femoral vein (drainage) **Femoral artery (infusion)**	**Femoral vein (drainage)** **Axillary artery (infusion)**	**Femoral vein (drainage)** **Carotid artery (infusion)**

Central venoarterial ECMO



Right atrium (drainage)
Ascending aorta (infusion)

Post cardiotomy - Cannulas of CPB are transferred to the ECMO circuit

Larger cannulas with low resistance

ECMO

V-V ECMO	V-A ECMO
Does not provide cardiac support	Provides cardiac support to assist systemic circulation
Connected in series	Connected in parallel
Low PaO2 achieved - •Blood with high oxygen saturation reaches the PA, ↑V/Q mismatch of the native lung due to the loss of hypoxic vasoconstriction •Recirculation of oxygenated blood within the circuit	Higher PaO2 achieved •artificially oxygenated blood mixes with arterial blood and directly perfuses distal organs •no loss of hypoxic vasoconstriction, in lungs
Less complications	More complications

INDICATIONS & CONTRAINDICATIONS

Indications of ECLS

- Hypoxic respiratory failure due to any cause
  - P/F ratio < 100 and/or Murray score ≥ 3
- Hypercapnic failure on MV despite high Pplat (pH <7.2)
- Need for intubation in a patient on lung transplant list
- Immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care)
- Refractory cardiogenic shock

ELSO General guidelines Ver 1.3 Dec 2013

Contraindications

- Mechanical ventilation at high settings (FiO2 > 0.9, P-plat > 30) for ≥ 7 days
- Major pharmacologic immunosuppression (absolute neutrophil count <400/mm^3)
- CNS hemorrhage that is recent or expanding
- Non recoverable co morbidity such as major CNS damage or terminal malignancy
- Age: no specific age contraindication but consider increasing risk with increasing age

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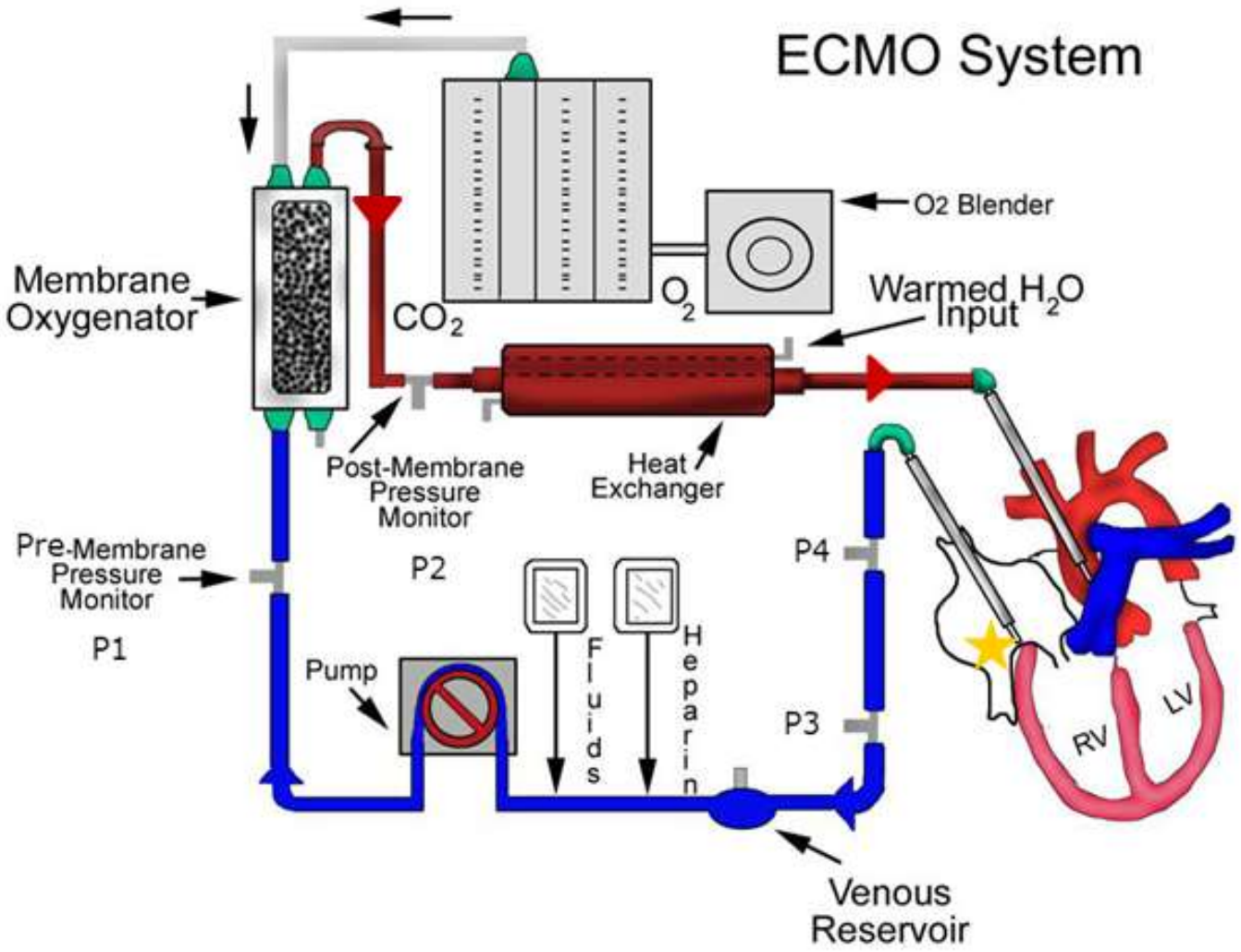
ECMO CIRCUITRY & COMPONENTS

ECMO circuitry



Components

- Cannulas
- Pumps
- Oxygenator /Membrane lung
- Heat exchanger
- Tubings

Components - Cannulas

- Best cannulation technique should be chosen on the basis of patients and clinical settings
- Intrathoracic or extrathoracic
- Percutaneous or surgical
- Percutaneous approach is standard of care in VV ECMO
  - Less risk of bleeding
  - Short operative time
  - Easier mobilization & nursing

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Cannulas

- Cannula size
  - Big enough to ensure adequate flow with relatively low suction pressure
  - Shouldn't exceed 2/3 rd of vessel diameter

- Positioning
  - Important to minimise recirculation
  - Tip should be in a high flow vessel

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Pumps

Roller pump	Centrifugal pump
Compresses the circuit tubing and pushes the blood through the raceway of the pump	Driven by electromagnetic induction motors and uses the principles of centrifugal force to generate a flow
Constant flow provided independent of circuit preload	Inability to maintain a set flow Back flow at low flow rates
Risk of cavitation and hemolysis Circuit disruption due to excessive pressure	Less risk of cavitation and air embolism Reduced blood trauma

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Oxygenator

- Blood and gas flow in counter-current directions within the silicone lung and gas exchange occurs by diffusion across the membrane
- Hollow fiber devices with polymethylpentene surface (PMP) replaced silicone ones
  - efficient at gas exchange
  - minimal plasma leakage
  - low resistance to blood flow

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components – heat exchanger

- Principle is counter current flow
- A great deal of heat is lost while a patient is on ECMO as a result of the large extracorporeal surface area to which the patient's blood is exposed
- The water is warmed to 37 ^{0}C to 40 ^{0}C to compensate for the heat loss in the circuit
- Kept less than 42 ^{0}C to prevent hemolysis and formation of bubbles

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Tubings

- Polyvinylchloride (PVC) – based plastic compound
- Minimal resistance to venous drainage
- Non-biologic surfaces of a circuit – activation of coagulation pathway and the inflammatory response
- Blood flow and pressure monitors
- Continuous oxyhemoglobin saturation monitors
- Circuit access sites

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Tubings

- Biocompatible lining to reduce the systemic inflammatory response and risk of thrombosis and bleeding
- Fewer the connectors and stopcocks – less is the flow turbulence and blood stasis

Laurance Lequier et al; Pediatr Crit Care Med. 2013

Components - Bridge

- Connection between the venous (drain) and arterial (return) components of the circuit
- Bypass to allow the isolation of the patient from the circuit
- If adequate gas exchange and hemodynamics can be maintained while flow continues through the bridge after its opening

INITIATION & MAINTENANCE

Technique of ECMO

- Should only be performed by clinicians with training and experience in its initiation, maintenance, and discontinuation
- The patient is anticoagulated with IV heparin
- Cannulae are inserted into the vessels
- Cannulae are connected to the limbs of circuit
- ECMO support is initiated after that

Gattinoni et al. Critical Care 2011, 15:243

S Allen et al; Journal of Intensive Care Medicine 2011

Circuit initiation

- Flow rate: 50-80 cc/dry kg/min

- BF required during VV bypass for acceptable arterial oxygenation is usually 3 to 6 L/min, partially depending on the cardiac output of the patient, on hemoglobin concentration and on saturation
- Maximum initially, then lowest flow to maintain SaO2>80- 85% at rest vent settings in VV ECMO

Gattinoni et al. Critical Care 2011, 15:243

S Allen et al; Journal of Intensive Care Medicine 2011

Circuit initiation

- In contrast, the flow rate used during VA ECMO
  *high enough to provide adequate perfusion pressure and venous oxyhemoglobin saturation
  *low enough to provide sufficient preload to maintain left ventricular output

- Sweep gas flow is titrated to maintain $PaCO_2$ at 40 mmHg

Gattinoni et al. Critical Care 2011, 15:243
S Allen et al; Journal of Intensive Care Medicine 2011

Titration & targets

- An arterial oxyhemoglobin saturation
  - VA ECMO : > 90 % ;VV ECMO : 80-85%
- SvO2 25-30% less than SaO2, measured on the venous line
- Higher SaO2 targets would require high flows predisposing to volume overload and hemolysis in VV bypass
- Adequate tissue perfusion, as determined by the ABP, venous oxygen saturation, and blood lactate level

Gattinoni et al. Critical Care 2011, 15:243

S Allen et al; Journal of Intensive Care Medicine 2011

Oxygenation monitoring

- If the FIO2 of the sweep gas is 1, the expected PO2 in the output blood (PO2out) should be high (generally > 300 to 400 mm Hg)

- Drop in pO2 in post oxygenator blood

  Oxygenator failure

  Recirculation

Gattinoni et al. Critical Care 2011, 15:243

S Allen et al; Journal of Intensive Care Medicine 2011

Oxygenation monitoring

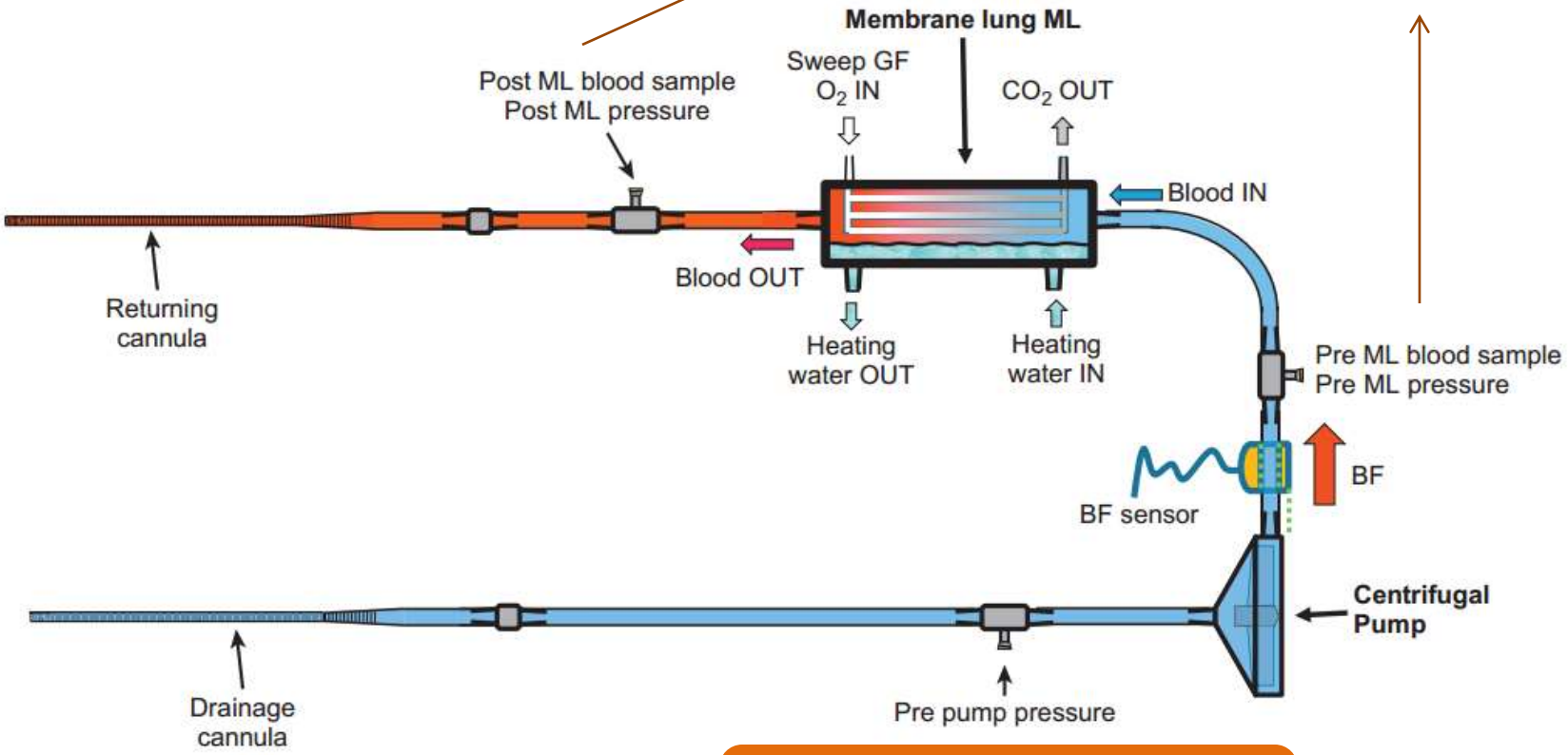
- Suspect recirculation
  - SaO2 below 80 % with reasonable ECMO flows
  - minimal improvement in saturation with higher flows
- Confirmed by decreased difference b/n pre and post oxygenator blood saturations
- Decreased by distancing the inflow and outflow cannula
- Even after readjusting, it can occur secondary to increased pulmonary vascular resistance leading to preferential flow thru ECMO circuit

Gattinoni et al. Critical Care 2011, 15:243

S Allen et al; Journal of Intensive Care Medicine 2011

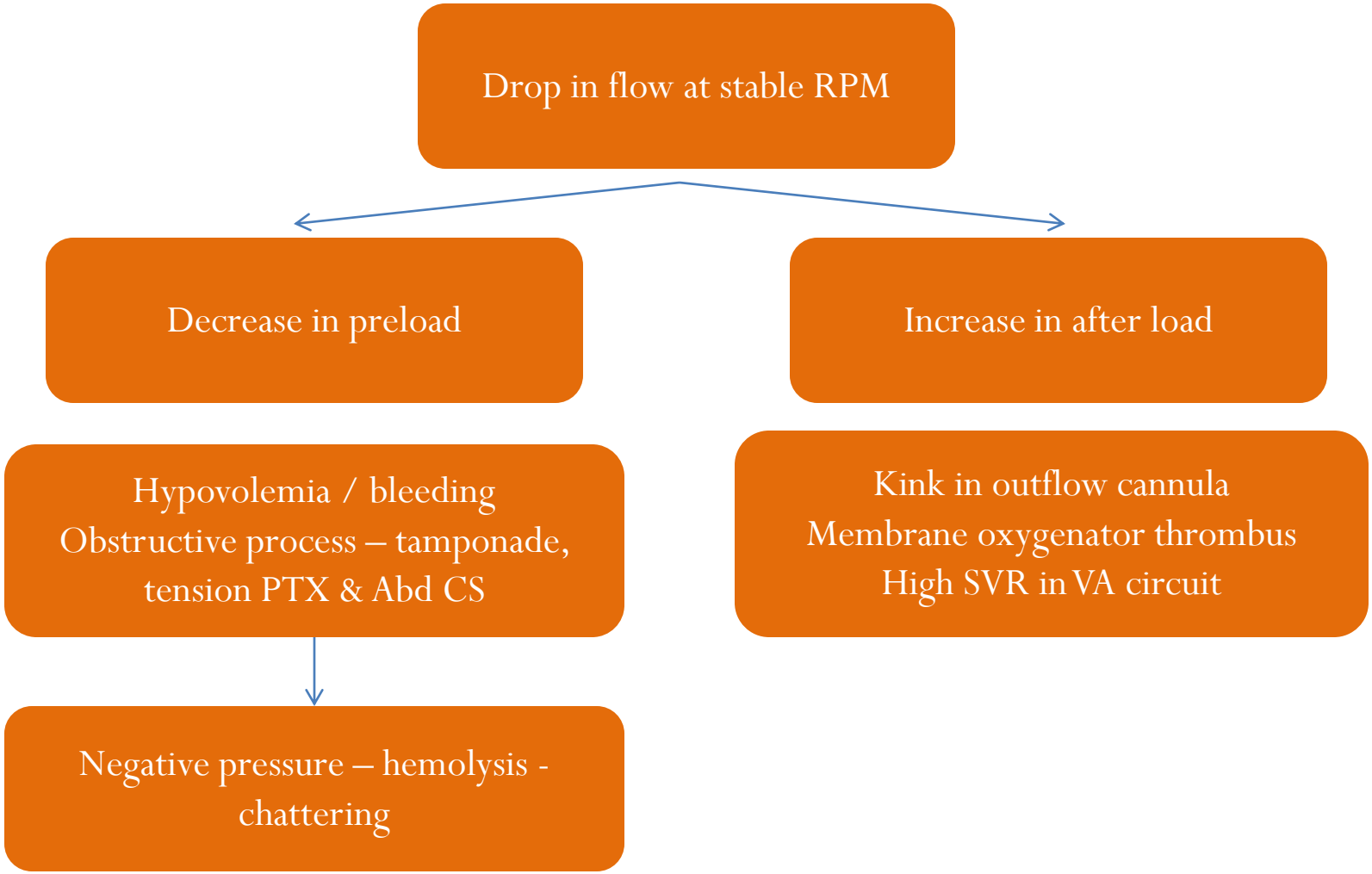
Pressure monitoring

Detect resistance in oxygenator (or) post oxygenator circuit



Ensure excessive suction is avoided

Flow monitoring



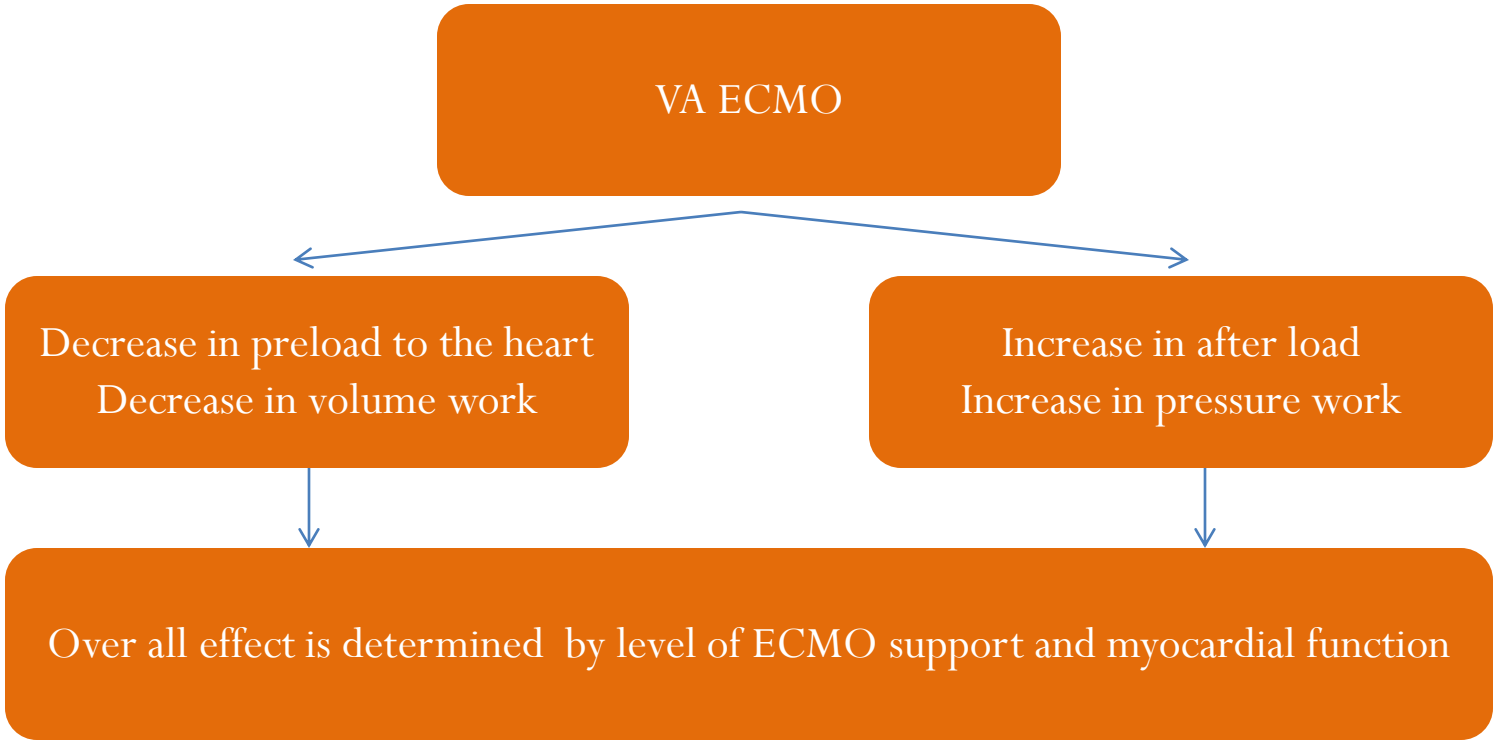
M Chung et al, ScientificWorld Journal 2014

MAP monitoring

- Essential in case of V A ECMO bypass - MAP > 65 mm Hg
- MAP should not exceed 90 mm Hg in order to limit the afterload
- MAP can be increased by administering the volume or by increasing the RPM
- Correction of volume status and vasopressor support as indicated to maintain MAP

M Chung et al, ScientificWorld Journal 2014

LV monitoring - V A ECMO



LV monitoring - V A ECMO

- Left ventricular output can be closely monitored by pulsatility in the arterial line's waveform & frequent echocardiography

- Insufficient unloading of the distended LV due to ongoing blood flow to LV from the bronchial circulation and right ventricle – pulmonary edema

M Chung et al, ScientificWorld Journal 2014

LV monitoring - V A ECMO

- Failing left ventricular contractility despite ECMO
  - Inotropic support
  - Intra aortic balloon pulsation

- Refractory LV depression
  - LV decompression
  - transatrial balloon septostomy or insertion of a left atrial or ventricular drainage catheter

M Chung et al, ScientificWorld Journal 2014

Systemic anticoagulation

- Intended to prevent thrombotic complications
- UFH most commonly used
- Classical dose is b/n 20 and 70 IU/kg/hr
- Sensitivity of UFH depends on endogenous AT3 levels and platelets
- If AT 3 deficiency, replace by FFP

Systemic anticoagulation

- ACT (activated clotting time) - standard of monitoring during heparin anticoagulation
- Target of ACT is 180 to 210 sec
- Target has to be individualised based on signs of hypo or hypercoagulability and ECMO flow rates
- Alternatives of ACT
  - PTT (1.5 times the baseline)
  - anti-Factor Xa activity (anti Xa) levels
  - thromboelastography (TEG)

Systemic anticoagulation

- Systemic anticoagulation in VV ECMO

  Systematic review, 18 studies including a total of 646 patients

  Rate of major bleeds was 16%

  Rate of clotting episodes was 53%

7 studies aPTT (n =199)	2 studies ACT (n =37)
Major bleeding episodes - 37 (19%) Major thromboses - 53 (27%)	Major bleeding episodes - 23 (62%) Major thromboses - 23 (62%)
aPTT targets ≥ 60 seconds (n =43, 5 studies) reported 24 (56%) bleeds & 3 (7%) clot aPTT target < 60 seconds(n = 156, 3 studies) reported 13 (8%) bleeds & 50 (32%) clots	

Michael C Sklar et al, Annals ATS. 2016

Systemic anticoagulation

- Optimal therapeutic targets for anticoagulation during ECMO are unclear
- Previously studies are retrospective, observational design, small cohorts, and patient heterogeneity
- Clinical significance of reported thrombotic complications is largely unknown
- Need for RCTs of anticoagulation strategies for patients undergoing ECMO

Michael C Sklar et al, Annals ATS. 2016

MV - ECMO

- Significant knowledge gap in understanding the benefits and risks of MV during ECMO
- Risk of VILI
  - Limitation of the alveolar strain by decrease in Vt
  - High PEEP with low Vt to prevent atelectrauma
  - Avoid oxygen toxicity to the lung from a high FiO2 & reabsorption atelectasis

Schmidt et al. Critical Care 2014, 18:203

MV - ECMO

- Cardiovascular effects
  - Increase in pulmonary vascular resistance, RV overload, causing adverse effects in pts of RV failure
  - Conversely, pts with predominately LV failure may develop pulmonary edema requiring high PEEP
  - ↓ lung perfusion may accelerate pulmonary vascular thrombosis in severe lung injury

Schmidt et al. Critical Care 2014, 18:203

MV - ECMO

- Most appropriate settings are unknown
- FiO2 <0.4
- Non damaging "rest settings (P plat<25 cm H2O)"
- Tidal volumes are maintained below 4 ml/kg PBW
- Increased alveolar recruitment with PEEP to maintain airway patency at low lung volumes

ELSO General guidelines Ver 1.3 Dec 2013

MV - ECMO

First 24 hrs	24 – 48 hrs	After 48 hrs
Moderate to heavy sedation	moderate to minimal sedation	Minimal to no sedation
PCV 25/15	PCV 20/10	PCV as before or take on PSV as the condition improves
I: E 2:1	I: E 2:1	
Rate 5/min	Rate 5/min + spontaneous breaths	
FiO2 0.5	FiO2 0.2 - 0.4	
FiN2 50 %	FiN2 60-80 %	

ELSO General guidelines Ver 1.3 Dec 2013

MV - ECMO

	European network	CESAR	EOLIA
Mode of MV	Volume AC	Pressure AC	Volume AC / APRV
PEEP	≥ 10	10 - 15	> 10
FIO2	0.3 – 0.5	0.3	0.3 – 0.6
Pressure limit	≤ 20 to 25 cm H_2O	20 to 25 cm H_2O	25 cm H_20
RR (/min)	6 - 20	10	10 - 30
Tidal volume	Targeted to above pressure	-	Targeted to above pressure

* To what extent we should reduce both the tidal volume and the plateau pressure to allow lung rest remains unknown

Transfusion support

- The benefit of enhanced oxygen delivery must be weighed against the potential harm of transfusion
- Many centers recommend transfusion who are receiving ECMO until their hematocrit levels are in the normal range
- Lesser blood flows in the circuit are required if hematocrit is maintained

Daniel Brodie NEJM 2011;365:1905-14.

Transfusion support

- Platelets are continuously consumed during ECMO because they are activated by exposure to the foreign surface area
- Platelet counts should be maintained greater than 50,000/microL, which may require platelet transfusion

Daniel Brodie NEJM 2011;365:1905-14.

Weaning from ECMO

- Progressive reduction of the ECMO contribution to oxygenation and CO2 removal as the gas exchange capability of the native lung improves and the patient's clinical conditions stabilize
- Requires regular monitoring the pts respiratory function (gas exchange function, respiratory mechanics) and hemodynamics

Steve Allen et al, Journal of Intensive Care Medicine 26(1) 13-26

Weaning from ECMO

- Respiratory failure
  - when 50% to 80% of total gas exchange is by the native lungs
  - when the patient's lung compliance improves
  - improving chest x-ray
- Cardiac failure
  - Enhanced aortic pulsatility correlates with improved left ventricular output
  - Decrease in mixed-venous oxygenation saturation
  - MAP> 60 mmHg in the absence of "high-dose" inopressors

Steve Allen et al, Journal of Intensive Care Medicine 26(1) 13-26

Weaning from ECMO

- VV ECMO trials
  - Sweep low rate is slowly decreased
  - Ventilator is placed on full support
  - Successful weaning is confirmed if the patient remains stable at a FGF of 0 L/min for a period of 4 to 24 hours

Steve Allen et al, Journal of Intensive Care Medicine 26(1) 13-26

Weaning from ECMO

- VA ECMO trials
  - Require temporary clamping of both the drainage and infusion lines, while allowing the ECMO circuit to circulate through a bridge between the arterial and venous limbs
  - If the patient manifests signs of deterioration, the bridge is clamped and flow is re-directed to the patient as before

Steve Allen et al, Journal of Intensive Care Medicine 26(1) 13-26

COMPLICATIONS

Complications ECLS

Circuit related complications

- Blood clots and thromboembolism
  - Failure of the oxygenator
  - Platelet consumption
  - Pulmonary or systemic embolism

- Gas entrapment and embolism
- Circuit fractures

Complications ECLS

Circuit related complications

- Recirculation – minimizing the oxygenation efficiency
- Shaking or "chatter" of the tubing - hypovolemia, cannula malposition, pneumothorax, and pericardial tamponade
- Manifests as caused by excessive negative pressure (created by the pump in the venous system) as well as a drop in pump output

Complications ECLS

Patient related complications

- Vascular access complications
  - Perforation of posterior wall, hematoma
  - Dissection of the vessel
  - AV fistula or pseudo aneurysm
- Leg ischemia in femoral arterial cannulation
  - Requires insertion of peripheral perfusion cannula distally

Complications ECLS

Patient related complications

- Bleeding – surgical site, GI, airway bleed
- Coagulopathy (TCP, HIT & DIC)
- Neurologic complications – intracranial hemorrhage
- Cardiac complications – insufficient unloading of the distended LV due to ongoing blood flow to LV from the bronchial circulation and right ventricle
- Sepsis

Complications ECLS

	Neonate (%)	Pediatric (%)	Adult (%)
Respiratory			
Mechanical: pump malfunction	1.6	2.2	1.5
Mechanical: oxygenator failure	5.7	10.6	9.1
Cannula hemorrhage	7.9	18.3	13.2
Surgical hemorrhage	6.3	12.6	10.5
Pulmonary hemorrhage	4.5	8.1	6.1
CNS hemorrhage	7.6	6.4	3.9
CNS infarction	6.8	4.2	2.0
Renal failure	7.8*	12.9*	9.3†
Hyperbilirubinemia	7.3	5.2	8.7
Infection	5.8	16.8	17.5

RR Thiagarajan et al, ELSO regitry, ASAIO Journal 2017

ECMO – ARDS

ECMO in ARDS

- Currently a salvage therapy for the most severe cases of ARDS
- Benefit of ECMO as compared to conventional, standard of care management for ARDS has yet to be demonstrated
- Increasing potential for ECMO to enhance the way ARDS is managed

M Parekh et al; Ann Transl Med 2017

Benefit in ARDS

- Complete lung rest – Lung protective ventilation
- Complete avoidance of VILI
- Adequate gas exchange extracorporeally
- Decreases Oxygen toxicity to lung

M Parekh et al; Ann Transl Med 2017

Indications in ARDS

* *Threshold for the initiation of ECMO varies considerably across studies and guidelines*

- Severe hypoxemia (P/F ratio <80, despite the application of high PEEP) for at least 6 hr in patients with potentially reversible respiratory failure
- Considered after a shorter interval if P/F ratio < 50
- Uncompensated hypercapnia with acidemia (pH <7.15)
- Murray score > 3.0

Daniel Brodie N Engl J Med 2011;365:1905-14

Contraindications in ARDS

- High-pressure ventilation (Pplat > 30 cm of water) or high Fio2 requirements (> 0.8) for >7 days
- Limited vascular access
- Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
- Any condition that precludes the use of anticoagulation therapy

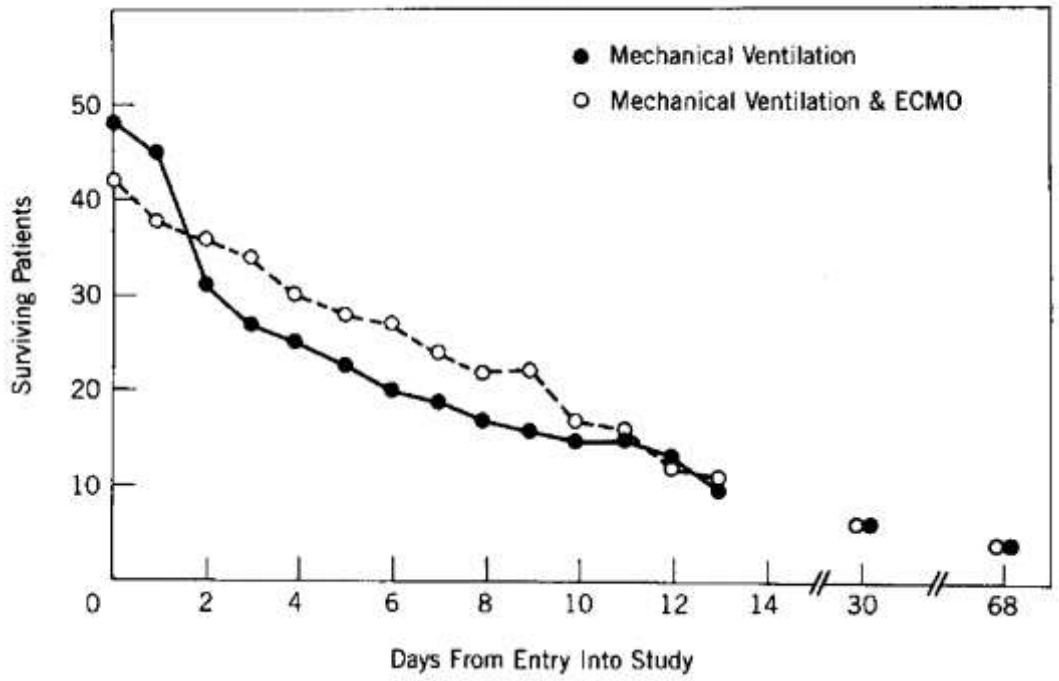
Daniel Brodie N Engl J Med 2011;365:1905-14

ECMO

- First prospective randomised study in severe ARF
- 9 medical centres, 90 subjects
- Majority - acute bacterial or viral pneumonia (57%)
- Conventional MV (n=48) *Vs* MV + VA ECMO (42)
- MV before entry 7 days in control group vs 9.6 in test group
- 4 survived in each group

ZapolWM et al, JAMA 1979;242(20):2193–2196

ECMO



Pts had significantly high PaO2, low PaCO2 in study group
Reduction of FiO2 from 0.74 to 0.48 seen in ECMO group
High mean daily transfusion support (1 to 2.5 L)
ECMO can support respiratory gas exchange but did not increase the probability of long-term survival in patients with severe ARF

ECMO

- 122 ARDS pts ($PaO_2 \leq 80$ mm Hg on $FiO_2 \geq 0.6$)
- Followed a predefined clinical algorithm
- Initially treated with advanced non invasive Rx options (PCV with PEEP, PHC, Reduction of pulmonary edema, optional proning and iNO)
- Those who are not responding to advanced Rx were taken onto VV ECMO by certain entry criteria

Lewandowski K et al, Intensive Care Med 1997, Aug;23(8):819-35

ECMO

- 122 consecutive patients according to a predefined treatment algorithm [(n=73), mean P/F 86] or to care involving ECMO [(n=49), mean P/F 67]
- The overall survival rate was 75%
- *89% in the AT-sine ECMO group & 55% in the ECMO treatment group ($p < 0.001$)*
- Patients in the ECMO group were found to have higher severity of illness scores and worse oxygenation at baseline

Lewandowski K et al, Intensive Care Med 1997, Aug;23(8):819-35

ECMO

- Evidence from these studies suggested no definite benefit of ECMO over conventional mechanical ventilation
- Its usage was restricted to clinical trials and not got widely implemented
- However these studies have little relevance now due to changed ventilatory strategies, ECMO circuits, disease management and increased experience with it

H1 N1 Australia NZ report

- Retrospective study of ECMO receivers for H1 N1 ARDS in 15 ICUs from June to August 2009
- 68 patients were included
  - 53 patients (78%) were PCR /viral culture positive
  - 8 patients (12%) had serological evidence of recent influenza A
  - 7 patients (10%) had preceding symptoms of influenza like illness

Andrew R Davies et al, JAMA, Nov 2009;Vol 302, No. 17

H1 N1 Australia NZ report

Characteristics	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Ventilation parameters, median (IQR)			
Lowest PaO_2/FIO_2 ratio	55 (48-65)	57 (45-62)	56 (48-63)
Highest FIO_2	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Highest PEEP, cm H_2O	18 (15-20)	15 (14-18)	18 (15-20)
Highest peak airway pressure, cm H_2O	36 (34-40)	34 (29-36)	36 (33-38)
Lowest pH	7.2 (7.1-7.3)	7.2 (7.1-7.3)	7.2 (7.1-7.3)
Highest $PaCO_2$, mm Hg	69 (54-86)	67 (61-73)	69 (54-83)
Highest tidal volume, mL/kg	5.6 (4.8-6.6)	5.7 (4.4-6.7)	5.6 (4.6-6.7)
Quadrants of radiograph infiltrate, No.	4 (4-4)	4 (4-4)	4 (4-4)
Acute lung injury score[a]	3.8 (3.3-4.0)	3.5 (3.3-3.8)	3.8 (3.5-4.0)
Pneumothorax pre-ECMO, No. (%)	9 (17)	1 (7)	10 (15)
Rescue ARDS therapies used, No. (%)			
Recruitment maneuver	30 (66)	8 (66)	38 (67)
Prone positioning	11 (22)	1 (8)	12 (20)
High-frequency oscillation	3 (6)	0	3 (5)
Nitric oxide	19 (38)	1 (8)	20 (32)
Prostacyclin	12 (23)	2 (15)	14 (22)

Andrew R Davies et al, JAMA, Nov 2009;Vol 302, No. 17

H1 N1 Australia NZ report

Outcome Measure	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Length of stay, median (IQR), d			
ICU	26 (16-35)	31 (15-38)	27 (16-37)
Hospital	35 (24-45)	40 (27-54)	39 (23-47)
Duration, median (IQR), d			
Mechanical ventilation	24 (13-31)	28 (13-34)	25 (13-34)
ECMO support	10 (7-14)	11 (10-16)	10 (7-15)
Survival at ICU discharge	38 (72)	10 (67)	48 (71)
Still in ICU	4 (8)	2 (13)	6 (9)
Survival at hospital discharge	22 (42)	10 (67)	32 (47)
Still in hospital[b]	14 (26)	2 (13)	16 (24)
Ambulant at hospital discharge[c]	21 (95)	10 (100)	31 (97)
SaO_2 on room air at hospital discharge, median (IQR), %[c]	97 (95-98)	97 (95-98)	97 (95-98)
Discharge destination			
Died	11 (21)	3 (20)	14 (21)
Home	18 (34)	4 (27)	22 (32)
Other hospital	0	1 (7)	1 (1)
Rehabilitation facility	4 (8)	5 (33)	9 (13)
Cause of death[d]			
Hemorrhage	3 (27)	1 (33)	4 (29)
Intracranial hemorrhage	4 (36)	2 (66)	6 (43)
Infection	1 (9)	0	1 (7)
Intractable respiratory failure	3 (27)	1 (33)	4 (29)

48 (71 %)

14 (21 %)

Andrew R Davies et al, JAMA, Nov 2009;Vol 302, No. 17

CESAR trial

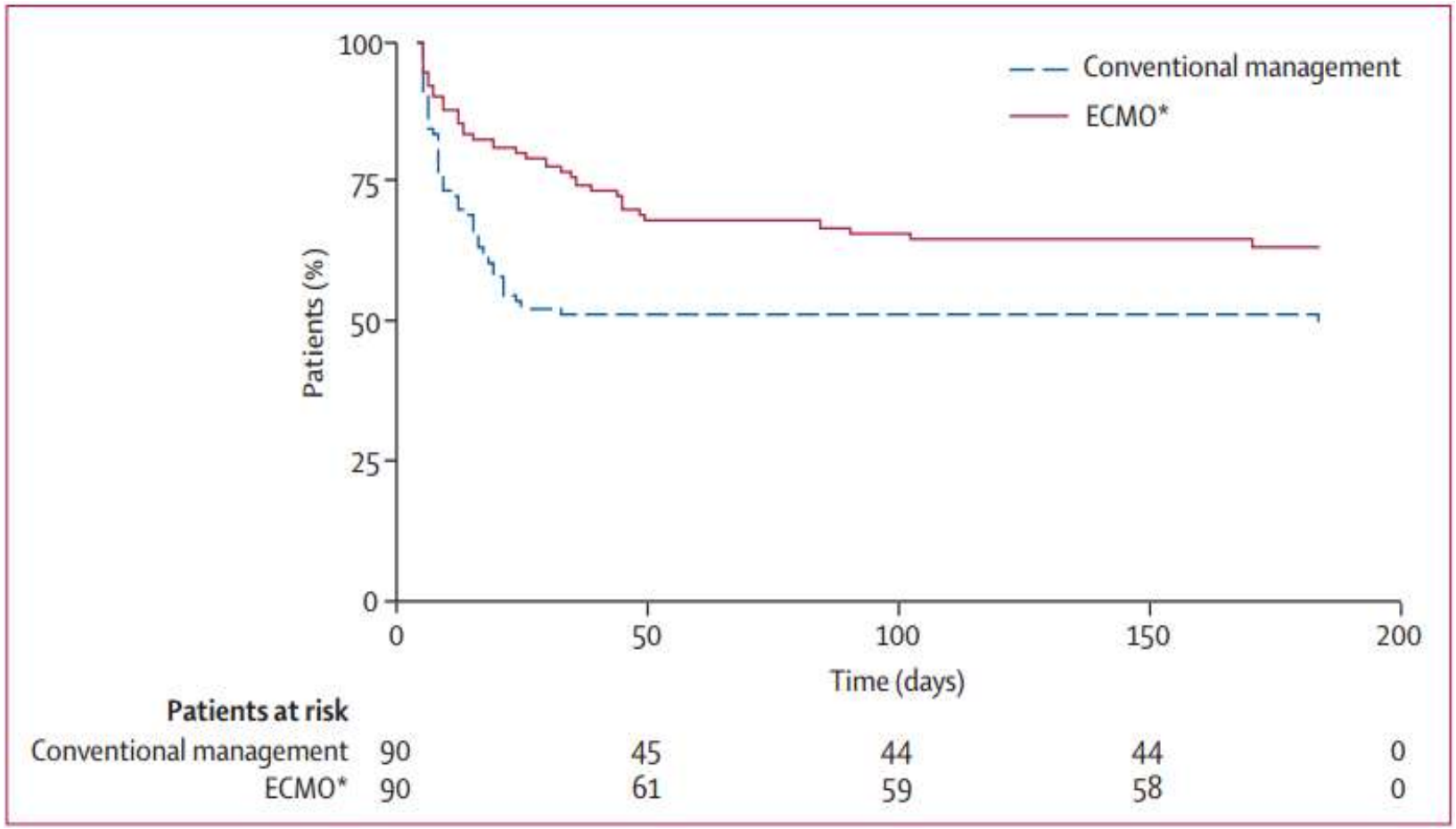
Efficacy of conventional ventilatory support versus ECMO for severe adult respiratory failure	
Participants	180 adults of severe but potentially reversible respiratory failure (Murray score ≥ 3.0 / pH < 7.2) despite optimal conventional Rx
Methods	Randomised in 1 : 1 fashion Conventional MV Vs Referral to consideration for ECMO 68/90 (75 %) received ECMO
Outcome measure	Death or severe disability at 6 m of randomisation
Results	Survival upto 6 months **63% (57/90) of ECMO** Vs **47% (41/87) of conventional MV** RR of 0·69; 95% CI 0·05–0·97, p=0·03)
Conclusion	Transfer of adult patients with severe but potentially reversible respiratory failure to a centre with an ECMO-based management protocol will significantly improve survival without severe disability

Giles J Peek et al;, Lancet 2009; 374: 1351–63

CESAR trial

	ECMO group (n=90)*	Conventional management group (n=90)	Relative risk (95% CI, p value)
Death or severe disability at 6 months	NA	NA	0·69 (0·05–0·97, 0·03)†
No	57 (63%)	41 (47%)‡	NA
Yes	33 (37%)	46 (53%)‡	NA
No information about severe disability	0	3 (3%)§	NA
Died at ≤6 months or before discharge	NA	NA	0·73 (0·52–1·03, 0·07)
No	57 (63%)	45 (50%)	NA
Yes	33 (37%)	45 (45%)	NA
Severe disability			
No	57 (63%)	41 (46%)	NA
Yes	0	1 (1%)	NA
Cause of death			
Respiratory failure	8 (9%)	24 (27%)	NA
Multiorgan failure	14 (16%)	15 (17%)	NA
Neurological disorder	4 (4%)	2 (2%)	NA
Cardiovascular disorder	1 (1%)	3 (3%)	NA
Related to ECMO	1 (1%)	0	NA
Other	1 (1%)	0	NA
Unknown	4 (4%)	1 (1%)	NA
Time between randomisation and death (days)	15 (3–41)	5 (2–14)	NA

CESAR trial



Giles J Peek et al; Lancet 2009; 374: 1351–63

Limitations - CESAR trial

- No standardisation of Rx protocol
  - 30% of the patients in control arm did not get LPV
  - Steroid recipients more in study group

Treatment by low-volume low-pressure ventilation strategy at any time	84 (93%)	63 (70%)	<0·0001
Time under strategy (days)	23·9 (20·4)	15·0 (21·1)	<0·0001
Steroids	76 (84%)	58 (64%)	0·001

Giles J Peek et al; Lancet 2009; 374: 1351–63

Limitations - CESAR trial

- Intervention in CESAR was *referral* to an ECMO center not *treatment* with ECMO
  - 25 % of patients in ECMO referral group didnot receive ECMO

- Two serious adverse events noted
  - Mechanical failure of O2 supply during transport
  - Vessel perforation during cannulation

Giles J Peek et al; Lancet 2009; 374: 1351–63

Limitations - CESAR trial

- Three patients died before they could be transferred and two died in transit
- Risk of death during transfer of such patients
- Exclusion of pts ventilated with high pressure or high FiO_2 for more than 7 days
- Did improved care at the single ECMO hospital lead to the relative risk observed??

Giles J Peek et al; CESAR trial, Lancet 2009; 374: 1351–63

ECMO

- UK H1N1 2009-10
- H1N1-related ARDS transferred for ECMO *Vs* matched patients who were not referred for ECMO
- Of 80 ECMO-referred patients, 69 received ECMO (86.3%) and 22 died (27.5%) prior to discharge from the hospital
- Survival to acute hospital discharge

Noah et al, JAMA 2011;306(15):1659-1668

ECMO

Deaths Analyzed by Matching Methods

	No. of Deaths/ Total No. of Patients (%)			
	ECMO-Referred	Non–ECMO-Referred	RR (95% CI)	*P* Value
Matching method				
Propensity score	18/75 (24.0)	35/75 (46.7)	0.51 (0.31-0.84)	.008
GenMatch	18/75 (24.0)	38/75 (50.7)	0.47 (0.31-0.72)	.001
Individual	14/59 (23.7)	31/59 (52.5)	0.45 (0.26-0.79)	.006

Abbreviations: ECMO, extracorporeal membrane oxygenation; RR, relative risk.

*For patients with H1N1-related ARDS, referral and transfer to an ECMO center was associated with lower hospital mortality compared to matched ones

Noah et al, JAMA 2011;306(15):1659-1668

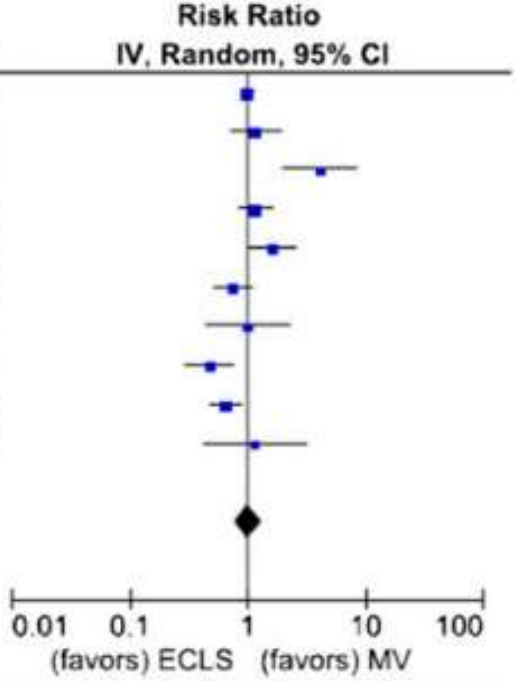
ECLS – In hospital mortality

- 4 RCTs, 6 observational studies(496/1248)

Study or Subgroup	ECLS Events	ECLS Total	MV Events	MV Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Zapol 1979	38	42	44	48	14.8%	0.99 [0.87, 1.12]	1979
Morris 1994	14	21	11	19	10.0%	1.15 [0.71, 1.88]	1994
Lewandowski 1997	22	49	8	73	7.1%	4.10 [1.99, 8.45]	1997
Mols 2000	28	62	71	183	12.3%	1.16 [0.84, 1.62]	2000
Beiderlinden 2006	15	32	34	118	10.4%	1.63 [1.02, 2.59]	2006
Peek 2009	25	68	44	90	11.7%	0.75 [0.52, 1.10]	2009
Roch 2010	5	9	5	9	6.1%	1.00 [0.44, 2.29]	2010
Noah 2011	18	75	38	75	10.4%	0.47 [0.30, 0.75]	2011
Pham 2013	35	98	54	98	12.5%	0.65 [0.47, 0.89]	2013
Bein 2013	7	40	6	39	4.8%	1.14 [0.42, 3.08]	2013
Total (95% CI)		**496**		**752**	**100.0%**	**1.02 [0.79, 1.33]**	
Total events	207		315				

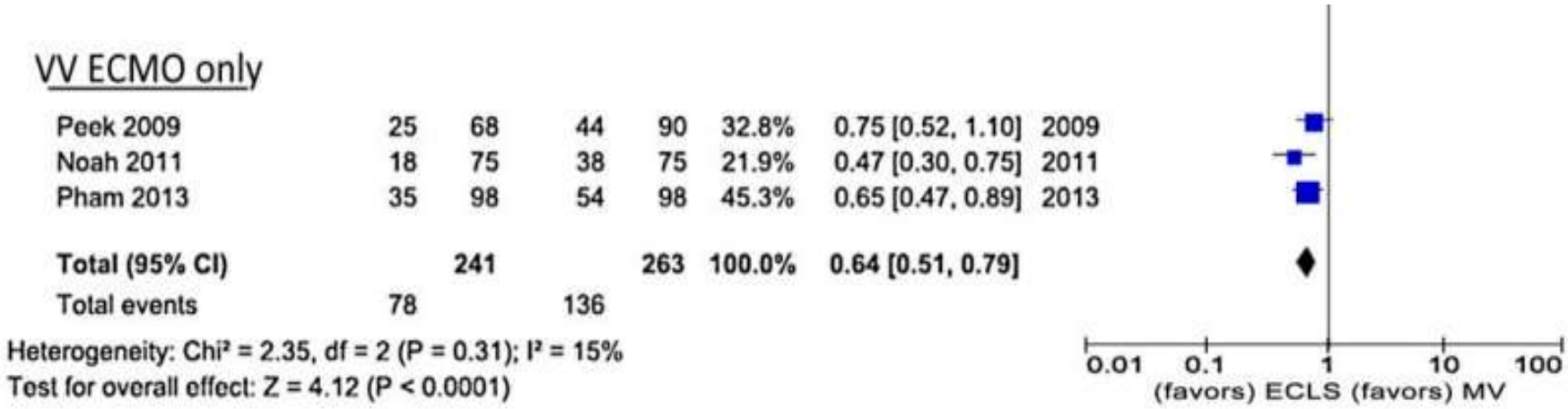
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 38.94$, df = 9 ($P < 0.0001$); $I^2 = 77\%$

Test for overall effect: Z = 0.17 (P = 0.87)



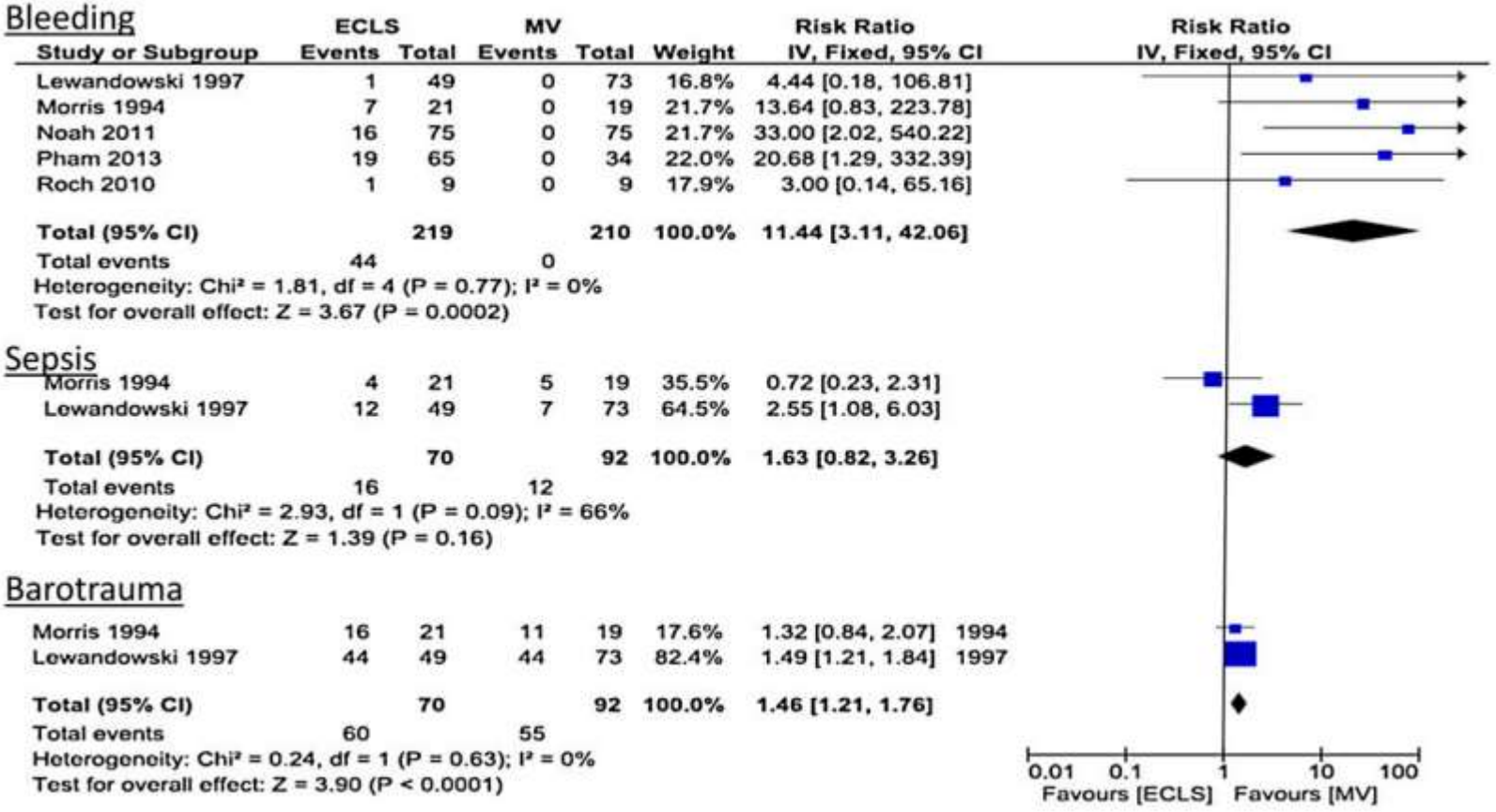
Laveena Munshi et al, Annals ATS 2014

ECLS – In hospital mortality



Laveena Munshi et al, Annals ATS 2014

ECLS – complications



Laveena Munshi et al, Annals ATS 2014

ECLS mortality

- Systematic review of 56 studies
- Mortality rates range from 36 to 56% in the studies performed in the last 15 years and reporting outcomes of >30 ECMO patients
- Mortality rates for H1N1 ARDS ranged from 14 to 64% in the 16 studies from 11 countries

Schmidt et al. Critical Care (2015) 19:99

ECLS mortality

- Factors associated with poor outcomes after ECMO for acute respiratory failure
  - Older age
  - More days of mechanical ventilation before ECMO
  - More number of organ failures
  - Low pre ECMO respiratory system compliance
  - Immunosuppression

Schmidt et al. Critical Care (2015) 19:99

Respiratory ECMO survival prediction (RESP)

Parameter	Score
Age, yr	
18 to 49	0
50 to 59	−2
⩾60	−3
Immunocompromised status*	−2
Mechanical ventilation prior to initiation of ECMO	
<48 h	3
48 h to 7 d	1
>7 d	0
Acute respiratory diagnosis group (select only one)	
Viral pneumonia	3
Bacterial pneumonia	3
Asthma	11
Trauma and burn	3
Aspiration pneumonitis	5
Other acute respiratory diagnoses	1
Nonrespiratory and chronic respiratory diagnoses	0
Central nervous system dysfunction†	−7
Acute associated (nonpulmonary) infection‡	−3
Neuromuscular blockade agents before ECMO	1
Nitric oxide use before ECMO	−1
Bicarbonate infusion before ECMO	−2
Cardiac arrest before ECMO	−2
Pa_{CO_2}, mm Hg	
<75	0
⩾75	−1
Peak inspiratory pressure, cm H_2O	
<42	0
⩾42	−1
Total score	−22 to 15

Schmidt et al, AJRCCM 2014

Respiratory ECMO survival prediction (RESP)

Derived from ELSO Registry (n =2355) 2000 to 2012

Hospital Survival by Risk Class		
Total RESP Score	**Risk Class**	**Survival**
⩾6	I	92%
3 to 5	II	76%
−1 to 2	III	57%
−5 to −2	IV	33%
⩽−6	V	18%

Schmidt et al, AJRCCM 2014

ECCO2 REMOVAL / RESPIRATORY DIALYSIS

ECCO2 removal

- Technique providing artificial respiratory support by removal of CO2 from blood through an extracorporeal gas exchanger
- Feature of other ECLS

- *Low flow VV or AV devices* – provide CO2 removal without oxygenation

History

- 1976 - *Kolobow and Gattinoni* explored the possibility of treating severe respiratory failure using low frequency PPV alongside ECCO2 removal in sheep
- 1986 – first clinical study on V-V ECCO2 removal by Gattinoni et al
- 1997 – first clinical study on A-V ECCO2 removal

Hypercapnia detrimental?

- Inhibition of cell membrane repair
- Suppression of innate immunity & host defence
- Uncoupling of RV & pulmonary circulation – RV failure
- Increase in intracranial pressure
- Depression of myocardial contractility

Morimont et al, Critical Care 2015, 19 : 117

Benefits of ECCO2R

- Decreases the detrimental effects of hypercapnia
- Better oxygenation
  - Increases the alveolar O2 concentration in accordance with the alveolar gas equation
  - By removing CO2, ECCO2R allows ventilation strategies that are focused on oxygenation rather than CO2 elimination
- "Rest lung" concept

Morimont et al, Critical Care 2015, 19 : 117

Benefits of ECCO2R

- COPD

  Obviates the need of intubation & IMV

  Facilitates withdrawal of IMV & extubation

- Weaning from MV
- Bridge to lung transplantation

Morelli et al, Intensive Care Med 2017, 43 : 519-30

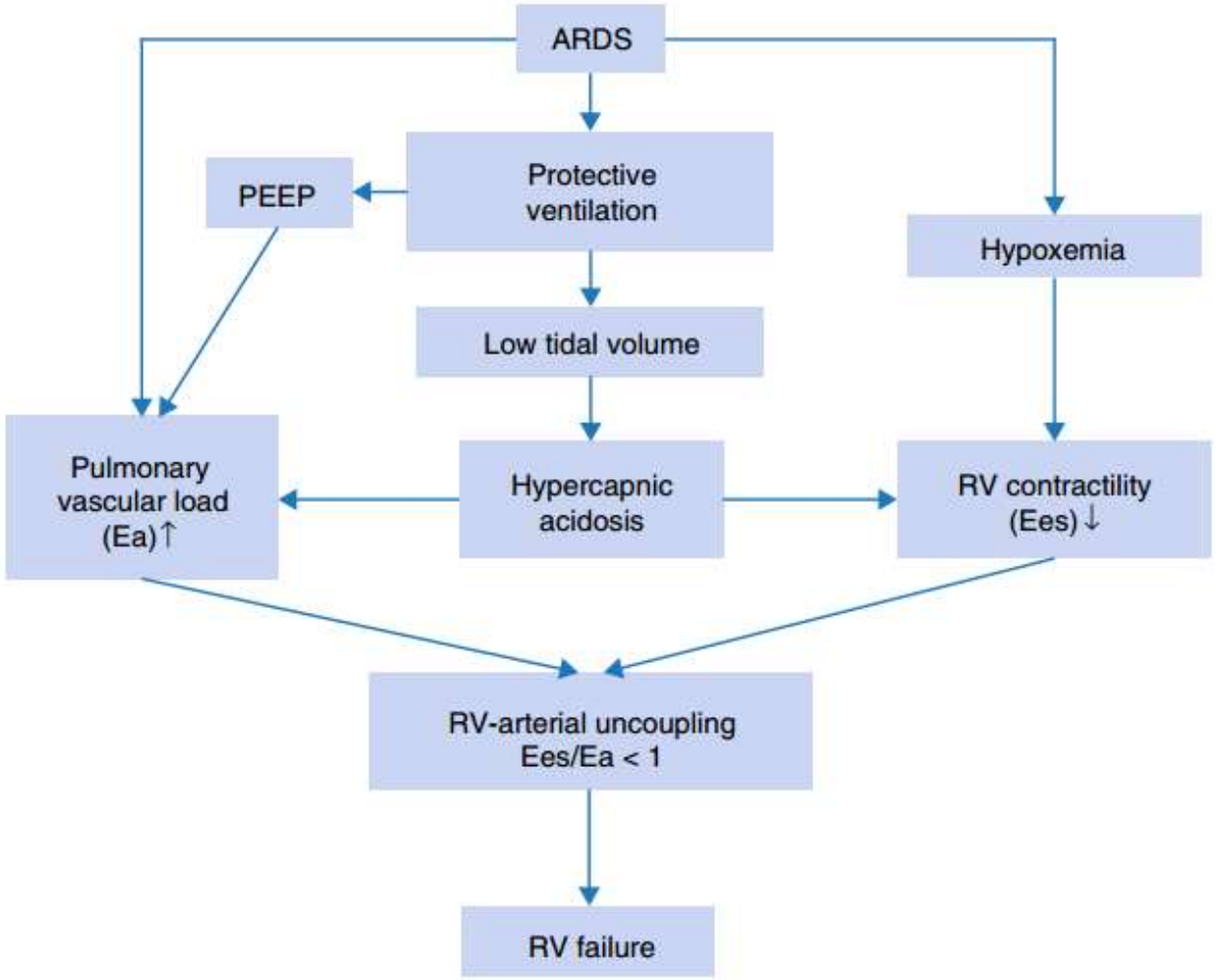
In ARDS…

- Decreases the ventilator induced lung injury (VILI) by allowing to ventilate the lung at low volumes and pressures
- Allows to continue low tidal volume ventilation (< 6 ml/kg IBW)
- Upto 50 % reduction in MV can be obtained while maintaining normocarbia

Morimont et al, Critical Care 2015, 19 : 117

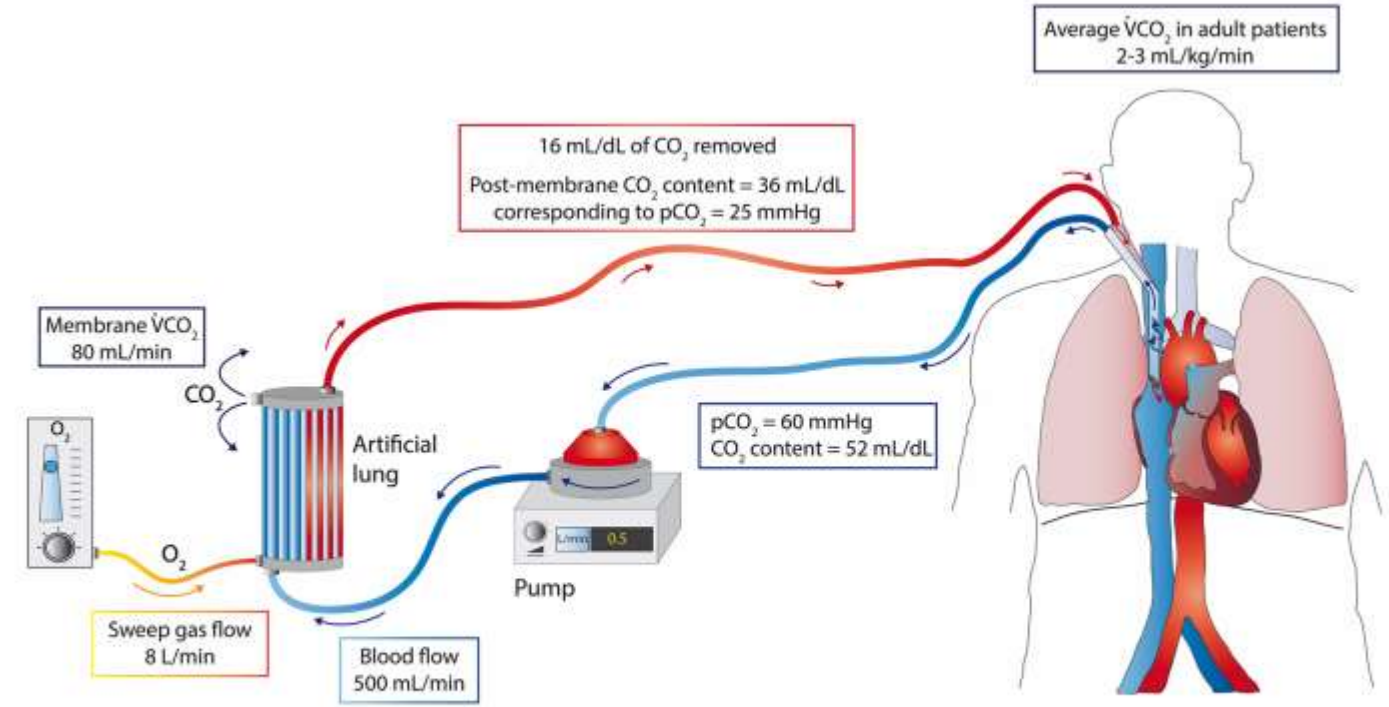
Morelli et al, Intensive Care Med 2017, 43 : 519-30

In ARDS…



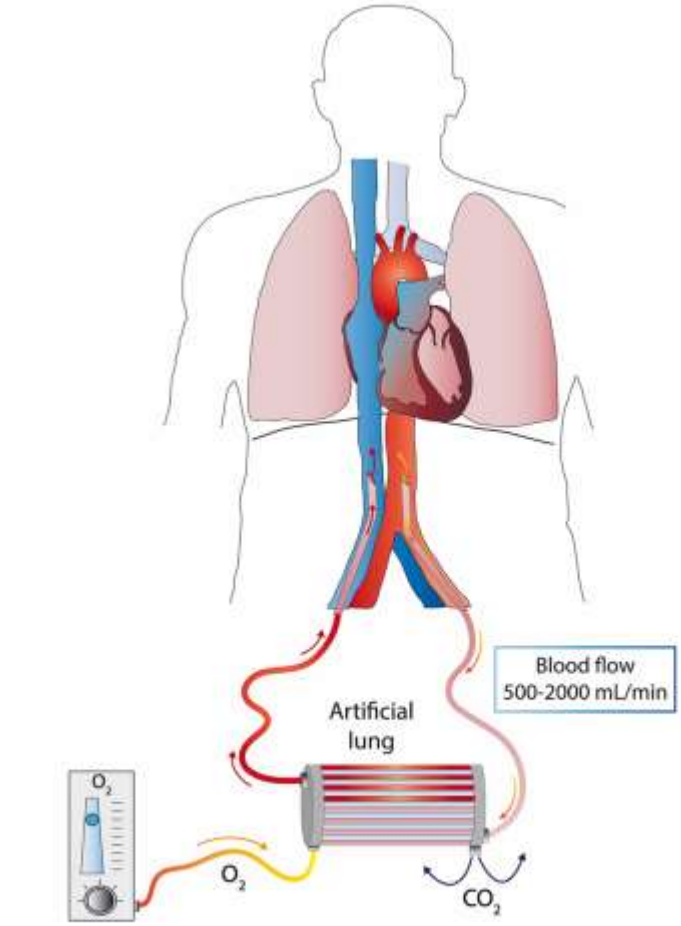
Morimont et al. Critical care 2015, 19:117

V –V ECCO2



VENO-VENOUS $ECCO_2R$
JUGULAR CANNULATION

A –V ECCO2



ARTERO-VENOUS $ECCO_2R$
FEMORAL-FEMORAL CANNULATION

Pumpless device
MAP of atleast 70 mm Hg
AV pressure gradient ≥ 60 mm Hg
Low resistance circuits

Higher cardiac index > 3 L/min /m^2
A proportion of CO doesn't affect the peripheral perfusion

Presence of hemodynamic instability / heart failure limits the use of such devices

Various devices

- The Pump-Assisted Lung Protection (PALP) (Maquet, Rastatt, Germany)
- The iLA Activve® (Novalung, Germany)
- The Hemolung® system (Alung Technologies, Pittsburgh, USA)
- The Decap® system (Hemodec, Salerno, Italy)

Complications of ECCO2 R

- Similar to ECMO
- Earlier had more complications in v/o large cannulas, complex circuits, high anticoagulation requirements
- A-V devices – Limb ischemia (ensure that the internal diameter of the artery is 1.5 times the external diameter of the cannula)
- V-V devices – thrombosis of the circuit

Evidence in ARDS

- Randomized controlled trial in 1994
- 40 patients of severe ARDS
- LFPPV - ECCO2 (21) vs conv MV (19)
- 30 day mortality
- No difference in survival in both {14/21(66.6%) *vs* 11/19 (57.9%)}
- 30% patients had severe hemorrhage

Morris et al, Am J Respir Crit Care Med 1994; 149:295-305

Evidence in ARDS

- The high mortality of $ECCO_2R$ in the early use were likely to be due to the complex extracorporeal systems with high flow resistances and large surface areas
- Use of occlusive roller pumps (high haemolysis rate)
- Less biocompatible membrane requiring high anticoagulation levels
- MV was in the pre-ARDSNet era and employed high tidal volumes and peak pressures

Morris et al, Am J Respir Crit Care Med 1994; 149:295-305

Evidence in ARDS

Tidal Volume Lower than 6 ml/kg Enhances Lung Protection	
Participants	Prospective study among 32 patients of ARDS who were ventilated ARDS protocol for atleast 72 hrs
Intervention	10 patients 28 ≤ P plat ≤ 30 cm H2O were placed on V-V ECCO2 device and progressive reduction in VT VT was reduced from 6.3 ± 0.2 to 4.2 ± 0.3 ml/kg, and Pplat decreased from 29.1 ± 1.2 to 25.0 ± 1.2 cm H2O ($P < 0.001$) PEEP was increased to attenuate the reduction of P/F ratio CT scan & BAL cytokine analysis was done before & after 72 hrs
Results	33.6 ± 6.3% reduction of Pa_{CO2} (from 73.6 ± 1.1 to 48.5 ± 6.3 mmHg) sufficient to normalize arterial pH (from 7.20 ± 0.02 to 7.38 ± 0.04) Decrease in poorly aerated & hyper inflated areas of lungs on CT BAL cytokines concentration significant reduction was seen

Terragni et al, Anaesthesiology 2009; 111:826–35

Evidence in ARDS

- Use of VT lower than 6 ml/kg PBW was a/w significant reduction of inflammatory and morphological markers of VILI
- Only observational study
- No control group of patients who received usual care without Lower *ARDSNet*/Carbon Dioxide Removal

Terragni et al, Anaesthesiology 2009; 111:826–35

Evidence in ARDS

LTV (3ml/kg) + AV ECCO2R Vs conventional LPV, *XTRAVENT* study	
Participants	79 patients of moderate/severe ARDS after 24 hrs stabilisation period
Intervention	Randomized to receive a low VT ventilation (3 ml/kg) + ECCO2 [or] ARDSNet strategy (6 ml/kg) PEEP following ARDSNet "high-PEEP/FIO2" table RR 10–25/min with an I: E ratio of 1:1
Outcomes	28-days and 60-days ventilator-free days (VFD)
Results	VFD's within 60 days were not different between the study group (33.2 ± 20) and the control group (29.2 ± 21,p = 0.469) Mortality rate did not differ between groups

Thomas Bein et al, Intensive Care Med (2013) 39:847–856

Evidence in ARDS

LTV (3ml/kg) + AV ECCO2R Vs conventional LPV			
	Av ECCO2-R (n =40)	*Control (n =39)*	*P*
VFD_28 days	10.0 ± 8	9.3 ± 9	0.779
VFD_60 days	33.2 ± 20	29.2 ± 21	0.469
LOS ICU (d)	31.3 ± 23	22.9 ± 11	0.144
LOS hospital (d)	46.7 ± 33	35.1 ± 17	0.113
In hospital mortality	7/40 (17.5 %)	6/39 (15.4 %)	1.000

Thomas Bein et al, Intensive Care Med (2013) 39:847–856

Evidence in ARDS

- In a post hoc analysis, ARDS patients who were more hypoxemic (P/F < 150) at baseline and who were treated with the low VT strategy had a significantly shorter ventilation period (28.2 ± 16.4 Vs 40.9 ± 12.8, *p=0.033*)
- No survival benefit was seen with LTV + ECCO2R

Thomas Bein et al, Intensive Care Med (2013) 39:847–856

Evidence in ARDS

Fanelli et al, Critical Care (2016) 20:36	
Participants	Prospective study among 15 patients of moderate ARDS
Intervention	VT was gradually reduced from 6 to a min value of 4 mL/kg by 0.5 mL/kg every 30 min & PEEP was increased to target a Pplat between 23 and 25 cmH2O If arterial pH was <7.25 with PaCO2 >60 mmHg, despite an increase in RR up to 35/min, ECCO2R device was switched on
Results	Initial reduction in VT, without ECCO2R resulted in significant respiratory acidosis (pH <7.25) in all significant reduction in Pplat from 27.7 ± 1.6 to 23.9 ± 1 cmH2O Mortality at 28 days was 47 %, which was expected 1/3 rd required either proning or ECMO for refractory hypoxia

Evidence in ARDS

- Systematic review
- 14 studies with 495 patients (two RCTs and 12 observational studies)
- No survival benefit seen in both RCTs
- More ventilator free days in P/F < 150 (Xtravent study)
- No difference in ICU LOS

Fitzgerald et al, Critical Care 2014,18 : 22

Evidence in ARDS

- All the studies showed reductions in tidal volume, peak inspiratory pressure, arterial partial pressure of carbon dioxide and increase in arterial pH
- Increased transfusion requirements were seen in couple of studies
- Lack of robust data supporting the use of these devices and their cost effectiveness

Fitzgerald et al, Critical Care 2014,18 : 22

Awaited…

- SUPERNOVA trial, ECCO2 removal combined with ultra low tidal volume MV in ARDS
- EOLIA trial (ongoing RCT, France), ECMO vs conventional MV for moderate to severe ARDS

Take home message

- Requires early & careful selection of patients with reversible disease and without significant comorbidities
- Rescue therapy for patients with severe ARDS
- Evidence of benefit in H1 N1 related ARDS
- VV ECMO – therapy of choice in ARDS
- ECCO2 R therapeutic adjunct in moderate to severe ARDS