Extracorporeal membrane oxygenation, an anesthesiologist’s perspective: Physiology and principles. Part 1

Sandeep Chauhan, Subin S
Department of Cardiac Anesthesia, C. N. C., All India Institute of Medical Sciences, New Delhi, India

ABSTRACT
Extracorporeal membrane oxygenation (ECMO) is an adaptation of conventional cardiopulmonary bypass techniques to provide cardiopulmonary support. ECMO provides physiologic cardiopulmonary support to aid reversible aspects of the disease process and to allow recovery. ECMO does not provide treatment of the underlying disease. The indications for ECMO support have expanded from acute respiratory failure to acute cardiac failure refractory to conventional treatments from wide patient subsets involving neonates to adults. Vascular access for ECMO support is either percutaneous through a single-site, dual-lumen bicaval cannula or transthoracic via separate cannulas. The modes of support are either veno-venous or veno-arterial ECMO. In this article, the physiologic aspects of ECMO support are outlined.

Key words: Cardiopulmonary bypass, extracorporeal membrane oxygenation, hemodynamic changes, oxygenation, physiology, venous–arterial ECMO, venous–venous extracorporeal membrane oxygenation

INTRODUCTION
Extracorporeal membrane oxygenation (ECMO) is a modified adaptation of conventional cardiopulmonary bypass techniques for prolonged cardiopulmonary support using intrathoracic or extrathoracic cannulation. ECMO is currently used at specialized centers to support patients with respiratory or cardiac failure who are unresponsive to conventional therapeutic interventions. Zwischenberger and Bartlett[1] proposed the term “extracorporeal life support” (ECLS) to describe prolonged but temporary (1–30 days) support of heart or lung function using mechanical devices. ECMO has now become a general byword for the wide range of methods that are in use for extracorporeal blood oxygenation and carbon dioxide removal. Problems in terminology of various methods and different modalities used have allowed the acronym ECMO to survive the changing technologies. Table 1 shows the acronyms used in various cardiac or pulmonary life support systems. Technically, ECMO terminology is used for modalities providing pulmonary support system involving oxygenation and carbon dioxide removal, and ECLS is used for both cardiac and pulmonary support systems, but these terminologies are still used interchangeably.[1,2]

HISTORY
ECLS and the development of the heart-lung machine in cardiac surgery by Dr. John H. Gibbon Jr. shared a common interwoven history and were primarily intended for pulmonary support. ECMO was introduced for the treatment of severe acute respiratory distress syndrome (ARDS) in the 1970s. Dr. Theodore Kolobow pioneered the perfection of flow patterns in the membrane lung, the

Table 1: Artificial cardiac or pulmonary support acronym

| Acronym | Description                          |
|---------|--------------------------------------|
| ECMO    | Extracorporeal membrane oxygenation  |
| ECLS    | Extracorporeal life support          |
| ECCR    | Extracorporeal carbon dioxide removal|
| PECO2   | Partial extracorporeal carbon dioxide removal|
| AVCOR   | Arteriovenous carbon dioxide removal |
| ECLA    | Extracorporeal lung assist           |
| IVOX    | Intravascular oxygenator             |

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Address for correspondence: Dr. Sandeep Chauhan, Professor, Department of Cardiac Anesthesia, C.N.C 7th Floor, A.I.I.M.S., New Delhi - 110039, India.
E-mail: sdeep61@yahoo.com
method of layering silicone and the design of vascular access catheters. The concept of heparin titration helped in reducing the bleeding complications, and the refined design of circuits with elimination of stagnant flow areas and incorporation of bladder systems redefined ECMO. Dr. Donald Hill in 1971 reported the survival of a 24-year-old polytrauma patient with ruptured aorta after a motorcycle accident, who even according to today’s standard would not have been considered a good ECMO outcome candidate, was successfully treated on ECMO during the acute phase of the disease. In the following few years, not much success in ECMO outcome and overall survival was seen in comparison to newer ventilatory management strategies. This had put ECMO in the backyard of management options with a failing repute. In 1972, clinical application of ECMO in respiratory failure of newborns and adults was attempted. There was revival of interest only after Dr. Robert H. Bartlett in 1976 reported the first neonatal ECMO survivor, baby Esperanza. This was the baby of a poor, illiterate peasant woman from Baja, Mexico. The mother was determined that her child would have a better life as a United States citizen, crossed the border and headed for Los Angeles. En route her membrane ruptured and she was taken to Orange County Medical Centre where her daughter was born. During delivery, the child had aspirated a large quantity of meconium and developed chemical pneumonitis. Even with maximal ventilatory support, the baby was unable to sustain adequate oxygenation. When the PaO2 decreased to 12 mmHg, the situation was considered so hopeless that there was nothing to lose. Dr. Robert H. Bartlett, a thoracic surgeon who had been involved in developing the membrane lung, wheeled in a machine from the laboratory. After 3 days of bypass, Esperanza, which means “hope”, was the name that the nurses gave this baby who recovered completely.[3-5]

To monitor the ECMO experience, an ECMO registry was established in 1980 at the University of Michigan. Dr. John Toomasain in 1984 created the Neonatal ECMO Registry. In 1989, charter for Extracorporeal Life Support Organization (ELSO) was formed with the purpose of stimulating multi-institutional research in the field of acute lung injury and its therapy. During the next two decades, the largest case series experience was registered by the ELSO voluntary case reporting registry. ECMO today is an accepted treatment modality for neonatal, pediatric and adult patients with respiratory and/or cardiac failure, failing to respond to maximal medical therapy or following heart surgery when there is an inability to wean from cardiopulmonary bypass or as a bridge to definitive therapy [Table 2].

**PHYSIOLOGY AND FUNDAMENTALS**

ECMO support is only useful in cases where the primary lung injury is accompanied by the absence of oxygen toxicity and barotrauma caused by mechanical ventilatory support, or the primary underlying cardiac insult is reversible. The fundamental problem accompanying the treatment modality which relies on the injured lung to maintain gas exchange is that the modality becomes gradually ineffective as the lung disease becomes more severe. The mortality increases from 33% with moderate lung injury to more than 82% with severe injury, secondary to continued barotrauma, volutrauma and oxygen toxicity, all combining to produce ventilator-induced lung injury. Criteria often cited for qualifying a patient for ECMO treatment are with pretreatment predicted mortality threshold reaching above 80-90%, shown by fulfilment of any of the criteria shown in Table 3.[6]

More frequently, indices to assess refractory hypoxemia are used. The arterial oxygen to alveolar oxygen ratio

| Table 2: Uses of extracorporeal membrane oxygenation |
|--------------------------------------------------|
| In children                                      |
| Neonatal respiratory failure                     |
| Pediatric respiratory failure                     |
| Cardiac failure                                  |
| In adults                                        |
| Respiratory failure                              |
| Cardiac failure                                  |

| Table 3: Extracorporeal membrane oxygenation indication indices for >80% predicted mortality |
|--------------------------------------------------------------------------------------------|
| Likely to die (predicted 80% mortality)                                                     |
| Oxygenation Index (OI) > 40 or > 35 for 4 hours                                             |
| OI = (MAP × FiO2 × 100) / PaO2                                                             |
| Ventilation Index (VI) > 90 for 4 hours                                                     |
| VI = RR × PIP − PEEP/1000                                                                  |
| Alveolar–arterial oxygen difference [(A − a)DO2] ×600 − 624 mmHg                           |
| (at sea level) despite 4–12 hours of medical management                                   |
| (A − a)DO2 = [atmospheric pressure − 47] − (PaCO2 + PaO2)/FiO2, 47 being vapor pressure at sea level |
| PaCO2 = carbon dioxide tension (partial pressure) of arterial blood                        |
| PaO2 < 50 mmHg for 2–12 hours (FiO2 of 100%)                                               |
| Acute deterioration PaO2 < 30–40 mmHg (FiO2 of 100%)                                       |
| pH < 7.25 for 2 hours                                                                      |
| Intractable hypotension                                                                    |

MAP = Mean airway pressure, FiO2 = Fractional inspired oxygen concentration, PaO2 = Oxygen tension (partial pressures) of arterial blood, RR = respiratory rate, PIP = peak inspiratory pressure, PEEP = peak end expiratory pressure
(a:A ratio < 0.15 at 12–72 hours) or alveolar–arterial oxygen tension gradient (A–a gradient > 450 for over 24 hours) can be used, but the oxygenation index (OI) is currently more commonly used [Table 3]. Mortality predictors are unfortunately derived by looking at retrospective data and tend to undermine the prediction of prospective results. However, due to the high technical demands, cost, and risk of complications (such as bleeding under anticoagulant medication), ECMO is usually only considered as a last resort therapy. It is imperative from the present evidence that the patient should be considered for the benefits from ECMO before the terminal ventilator lung injury, which occurs in 7–9 days depending on the patient’s age, coupled with the failure of conventional treatment.\(^7\)

Physiological goals of ECMO are: (1) Remove CO\(_2\) and oxygenate the blood; (2) Improve tissue oxygen delivery; (3) Allow normal physiologic metabolic milieu at tissue level; and (4) Provide lung rest and/or cardiac offloading.

**ECMO CIRCUIT**

The components include [Figure 1] a roller or impeller pump, a membrane oxygenator, a heat exchanger, polyvinylchloride connecting tubing, connectors and a bladder reservoir. Blood is driven through the membrane by the roller pump or centrifugal pump and passively drained by gravity from the venous circulation using a siphon height of 100 cm or more into a collapsible bladder that acts as a compliant reservoir. The bladder has a proximity switch attached to its surface and acts to regulate the roller pump by turning it off when the bladder deflates. The roller pump or centrifugal pump draws blood from the bladder and pushes it through silicone membrane oxygenator and then a heat exchanger before returning it to the patient. The bladder and pump are linked by a trip-switch mechanism so that if pump flow exceeds venous drainage, the bladder collapses to inhibit pump flow. This blood flow in the extracorporeal circuit requires systemic heparin administration to prevent thrombus formation within the circuit and membrane oxygenator.

**Anticoagulation on ECMO**

Heparin is required after arterial and venous cannulation, 100 IU/kg bolus followed by infusion of 125 IU/kg/hour to maintain an ACT at 180–200 s. Titration of appropriate anticoagulation with its antecedent clinical implications of bleeding and thrombosis remains the principal causes of mortality and morbidity. The vast differences in neonatal and adult anticoagulation and transfusion requirements demand tremendous clinical knowledge to provide the best care. Methods to recognize the level of thrombin formation at the bedside could help reduce thrombotic neurologic complications. ECMO requires an overall multidisciplinary team approach to achieve the best clinical outcome.

**Types of ECMO circuits**

Circuits for ECMO support can be broadly categorized into two types [Table 4]: veno-arterial (VA) and veno-venous (VV) ECMO.

Depending on the sole need to provide respiratory support to an additional cardiovascular support, it can be interchanged from VV to VA or veno-arterial-venous (VAV) ECMO.

**CARDIOVASCULAR RESPONSE ON ECMO**

Systolic and diastolic pressures decrease with decrease in aortic pulse pressure. Preload and afterload parameters are the most affected. Peak and mean blood flow velocities decrease by 30–50% after ECMO. They return to normal after 72 hours of ECMO run, concurrent with the reduction in pump flows. Blood pressure abnormalities occur frequently following the initiation of ECMO. Systemic hypertension is more frequent than hypotension. Initial management on ECMO requires the weaning of inotropes with aggressive treatment.
for hypertension, as there is a risk of intracranial hypertension and bleed (especially in neonates). Hypotension is less frequent, but is secondary to decrease in systemic vascular resistance and the most common cause is hypocalcemia. Arrhythmias are commonly encountered during cannulation for ECMO, particularly bradyarrhythmias secondary to vagal stimulation, hypoxia or acidosis. Other arrhythmias include atrial and ventricular ectopics from mechanical irritation. Atrial fibrillation and supraventricular tachycardia are less common but are usually responsive to cannulae repositioning. Electrolyte abnormalities of calcium and potassium can occur during the first hour of ECMO support and can contribute to rhythm abnormalities. Cardiac Stun, complete or near-complete absence of ventricular contractions in response to ECMO support (predominantly seen in VA ECMO), may spontaneously resolve, but carries a high mortality. Seen as pulse pressure becoming \(<5\) mmHg with a marked increase in \(\text{PaO}_2\) which almost equals membrane lung \(\text{PaO}_2\) and is hypothesized as reperfusion injury or mismatch of preload or afterload or contractility. This can also result from incorrect positioning of cannulae. In such scenarios, cannulae repositioning usually solves the issue.\(^{7-9}\)

### HEMODYNAMICS ON ECMO

**VA ECMO**

On ECMO support, blood flow is essentially nonpulsatile and the perfusion is reflected by the narrow pulse contour and the narrow pulse pressure. Blood flow during ECMO is maintained at 80% of the calculated total blood flow and the accepted pulse pressure is between 10 and 15 mmHg. When on total ECMO support, i.e. 100% of calculated flow, the left ventricle (LV) gradually distends from Thebesian return and ejects, leading to an occasional pulsatile beat; therefore, it cannot be sustained for long with normal cardiac function, necessitating the ECMO flows being reduced to 80% of total calculated flow. Pulse contour is therefore not physiologically important for gas exchange as long as the total blood flow is adequate. VA ECMO offloads and provides rest to right side of the heart. In patients with impaired LV function, distension even from Thebesian shunt flows can lead to subendocardial hypoperfusion.

During partial VA ECMO support, the important factor to be considered is the coronary artery blood flow being derived from native LV flow, which may be desaturated because of return from the bronchial flows. Also, the LV afterload is increased with the arterial cannula positioning into right brachiocephalic artery, directing blood into the aortic root, ultimately resulting in increased metabolic demand. Thereby, in this scenario, failing LV may not be rested on partial VA ECMO, during which the heart is exposed to an elevated preload, afterload and increased wall tension, resulting in an enhanced oxygen consumption and hypoxic coronary perfusion. Thus, higher ECMO flow rates may be required for LV decompression, for complete myocardial rest from any distension which thereby occur. Factors

### Table 4: Differences between veno-arterial and veno-venous extracorporeal membrane oxygenation

|                    | VA ECMO                      | VV ECMO                      |
|--------------------|------------------------------|------------------------------|
| Cannulation site   | Vein:<br>- Internal jugular<br>- Femoral<br>- Artery:<br>- Right common carotid<br>- Axillary<br>- Femoral<br>- Aorta | Single cannulation:<br>- Internal jugular<br>- Right atrium<br>Double cannulation:<br>- Jugular-femoral<br>- Femoro-femoral<br>- Sapheno-saphenous |
| Arterial \(\text{PaO}_2\) | 60–150 mmHg                  | 45–80 mmHg                   |
| Indicators of \(\text{O}_2\) sufficiency | - Mixed venous oxygen saturation (mSv\(\text{O}_2\))<br>- \(\text{PaO}_2\)<br>- Calculated oxygen consumption | - \(\text{SaO}_2\) and \(\text{PaO}_2\)<br>- Cerebral venous saturation<br>- Pre-membrane saturation trend |
| Cardiac effects    | Preload: decreased<br>Afterload: increased<br>Pulse pressure: lower<br>CVP: varies<br>Coronary \(\text{O}_2\): varies<br>- LV blood desaturated, - Cardiac Stun syndrome | May reduce RV afterload<br>Rest unaffected |
| \(\text{O}_2\) delivery capacity | High | Moderate |
| Circulatory support | Partial to complete | No direct support, increased \(\text{O}_2\) delivery to coronary and pulmonary circuit → improving cardiac output |

VA: Veno-arterial, VV: Veno-venous, ECMO: Extracorporeal membrane oxygenation
increasing oxygenation in VA ECMO are shown in Table 5, when no native lung function is present.[6-8]

Echocardiographic evaluation of cardiac performance shows unaltered diastolic dimensions of atria and ventricles, but the systolic dimensions of ventricular chambers increase along with a decrease in fractional shortening. LV circumferential shortening velocity decreases after ECMO initiation. These performance indices return to baseline as ECMO flow rates decrease. This decrease in cardiac performance index on ECMO initiation is secondary to an increase in afterload. The underlying mechanism is not clearly understood, but suspected role of renin–angiotensin–aldosterone activation is postulated. Peak and mean blood flow velocities which are normal prior to ECMO decrease by 30–50% after initiation and return to baseline by 72 hours. Right and left ventricular stroke volumes are nearly identical and vary inversely with pump flow rate. Total aortic flow, which is the sum of pump flow and ventricular cardiac output, remains the same with either an increase or a decrease in pump flow. In infants, ductus arteriosus is commonly patent and on ECMO showed a significantly longer run time compared to patients without patent ductus. The shunting pattern changes with resolution of lung pathology and is a useful monitor for clinical improvement. Furthermore, it is not clear how a hemodynamically important ductus arteriosus, also with potential stealing effect on the cerebral circulation from left to right shunt, should be treated (conservative, surgically or with medication). This warrants further studies on ECMO. [9-12]

### Veno-venous ECMO

In veno-venous (VV) ECMO, a double lumen venous cannula is used to remove blood from the right atrium (RA), which is then oxygenated and returned back to the RA through the distal lumen of the double lumen cannula [Figure 2]. VV ECMO does not support the circulation and hence no effects on hemodynamics are seen, as blood withdrawn from the RA is returned back into the RA. Since CO₂ is readily diffusible, relatively low VV flow is sufficient to remove CO₂. In VV ECMO, the mixed venous oxygen saturation is high. The oxygenation is blood flow dependent and more blood must pass through the oxygenator to achieve a good degree of oxygenation. Clinically, maintaining a hematocrit of >5% above normal on VV bypass helps to improve oxygenation [Tables 6–9]. This type of ECMO is suitable when adequate cardiac output reserve is present to compensate for hypoxia with the systemic O₂ delivery being just adequate enough to meet the systemic oxygen requirement.

VV ECMO increases oxygen flow to the pulmonary artery (PA), the increased blood flow increases pulmonary vascular resistance and increases RV afterload which may precipitate right ventricular myocardial stun. With pre-existing pulmonary hypertension, management strategies are directed against right ventricular afterload increase. The effects of higher oxygen saturation in the PA may decrease pulmonary vascular resistance and right ventricular afterload, along with avoidance of increased LV afterload, thereby improving coronary artery perfusion and LV performance. Three variables are used to monitor oxygenation during VV ECMO: 1) arterial oxygen saturation (SaO₂); 2)
mixed venous oxygen saturation (mSvO₂); and 3) preoxygenator O₂ saturation. SaO₂ is simple and readily available with easy interpretation. Preoxygenator O₂ saturation (determining factor for adequate oxygenation in VA ECMO) is interpreted on lines of mixed venous saturation because of recirculation. Table 10 shows the factors affecting recirculation with the use of double lumen cannula.

High SaO₂ values may be present despite the drop in mSvO₂ and O₂ delivery. An SaO₂ value <70% reflects suboptimal O₂ delivery. mSvO₂ taken from jugular bulb is not affected by recirculation and is not sensitive to cardiopulmonary status, but is sensitive to ventilation changes secondary to preserved cerebral blood flow even in situations of cardiopulmonary failure.

VV ECMO systems may actually recirculate previously oxygenated blood depending on the placement of the inflow and outflow catheters. Another variant of VV ECMO is extracorporeal CO₂ removal (ECCO₂R) and tidal-flow VV ECMO. In ECCO₂R, oxygenation is provided by slow ventilation of the native lungs while CO₂ removal is accomplished by the ECMO circuit. With tidal-flow VV ECMO, single site cannula allows for alternate to and fro blood flow in either direction. There is a combination of arterial and venous reservoir with an alternative tube clamping system to control drainage and reinfusion through the same cannula. In all forms of ECMO, CO₂ removal is more efficient than O₂ addition because of the higher solubility and faster diffusion properties of CO₂ relative to O₂. In fact, CO₂ normally has to be added to ECMO circuits to offset this efficiency of CO₂ removal. The flow through the ECMO circuit is typically on the order of 100 ml/kg/minute. This flow is 25–75% of the cardiac output. This high flow requires the placement of cannula with large internal diameter and shorter length to allow for higher extracorporeal flow. Line pressure up to 300 mmHg is considered safe, although at higher pressures, higher chances of blood leaks, circuit breaks with disruption and hemolysis exist. Current circuits require the use of systemic anticoagulation with heparin to keep the systems patent. This anticoagulation to a large extent is responsible for bleeding complications that can be seen with the use of ECMO. Bleeding may occur either at the site of catheter insertion or at a remote site such as intracranial or the gastrointestinal tract. Future catheters with impregnated heparin may obviate the need for systemic anticoagulation and would be expected to reduce bleeding complications. Once blood leaves the patient, it comes in contact with a gas-permeable membrane that allows gas exchange to occur between the blood and the gases (oxygen and carbon dioxide) that are run into the oxygenator. CO₂ levels leaving the oxygenator can be adjusted about as low as the physician wants, while oxygen levels typically reach the 400–500 mmHg level. It is notable that the CO₂ content varies fairly directly with partial pressure while O₂ content follows the shape of the oxyhemoglobin dissociation curve. Under normobaric conditions, this limits the amount of oxygen that can be loaded into the blood.[13-15]

Veno-arterial-venous ECMO

It provides systemic perfusion as in VA ECMO (heart and lung support), and is done in VV ECMO with the addition of an arterial cannula. This transformation from VV to veno-arterial-venous (VAV) is initiated

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Table 6: Targets on vено-venous extracorporeal membrane oxygenation

| Target                                      |
|---------------------------------------------|
| SaO₂ 85–95%                                 |
| PaO₂ 45–55 mmHg                             |
| Hematocrit >5% of normal baseline          |

Table 7: Factors increasing oxygenation on vено-venous extracorporeal membrane oxygenation

| Factor                                      |
|---------------------------------------------|
| Increasing ECMO flow (no change in systemic flow) |
| Decreasing % of recirculated flow           |
| Increased hemoglobin                        |
| Increased mixed venous oxygen (decreased oxygen consumption) |
| Increased cardiac output                    |

Table 8: Advantages of vено-venous extracorporeal membrane oxygenation

| Advantage                                      |
|-----------------------------------------------|
| Avoids ligation of carotid artery             |
| Thromboembolism to systemic artery avoided    |
| Decreased risk of neuronal injury             |
| Decreased potential for ischemic lung injury  |
| Preserves normal physiological pulsations     |

Table 9: Variants of vено-venous extracorporeal membrane oxygenation

| Variant                                      |
|----------------------------------------------|
| Single site cannulation                      |
| Two site cannulation                         |
| Extracorporeal CO₂ removal (ECO₂R)           |
| Tidal flow VV ECMO                           |

Table 10: Factors affecting recirculation with double lumen cannula

| Factor                                      |
|---------------------------------------------|
| Pump flow: Recirculation increases linearly (from negative suction) with increasing pump flow. |
| Catheter position: High in superior venacavae, increased recirculation. |
| Cephalic catheter: Decreased recirculation and increased oxygen delivery[15] |
| Cardiac output: Increased CO₂, decreased recirculation (better forward flow) |

CO: Cardiac output
on hemodynamically unstable patients for providing cardic support [Table 11]. During the VAV ECMO run, there should be no persistent acidosis or base deficit and the lactate levels should be normal, similar to patients managed on VA ECMO. By increasing blood flow, lower oxygen saturations or arterial gases can be accepted, if the perfusion parameters are acceptable.

**PHYSIOLOGY OF OXYGEN EXCHANGE ON ECMO**

Oxygen delivery on ECMO is determined by a combination of blood oxygenation within membrane lung, flow through the extracorporeal circuit, oxygen uptake through the native lung and cardiac output through the native heart. The final oxygen gradient at tissue level is determined by extracellular tissue partial pressure of O$_2$ (normal 30 mmHg) to reach cell cytoplasmic partial pressure of oxygen (normal 6–10 mmHg) required for optimal metabolic requirement. Oxygen transport in the oxygenator occurs across a semipermeable membrane, from the gas interface to blood interface. Here, the oxygen gradient is relatively large, making the diffusion across the thin silicone membrane relatively swift. The critical factor for oxygen delivery is the blood phase. The longer the blood is in contact with the membrane, the better is the saturation of hemoglobin with oxygen. Therefore, a minimum time is required for oxygenation. Also, a laminar flow will cause better oxygenation of blood at the sides of membrane than the blood at center column. Hence, any mechanism disrupting the laminar flow would result in better oxygenation efficiency. Finally, larger the surface area, larger is the area for oxygenation. As the blood path thickness and surface area of membrane is fixed, this makes a limitation for achieving maximal blood flow, ultimately restricting the O$_2$ transmission across the membrane. Rated flow is the pump flow at which maximal oxygen delivery is achieved and is unique to each membrane oxygenator device. Tables 12 and 13 show important variables for oxygen exchange that relate to oxygen gradient between the blood and gas phases. In critically ill patients, particularly the pediatric group, oxygen consumption may increase from 6–8 ml/kg/min to about 10–12 ml/kg/min or higher during seizures, sepsis and with infusion of catecholamine drugs. This may require higher flows on ECMO run to meet the oxygen requirement.[13-15]

CO$_2$ transport- CO$_2$ transport is 20 times more efficient than the oxygenation in the lungs; this principle applies even to artificial lungs. The most important factor limiting the transfer of CO$_2$ [Table 14] is the relative concentration of CO$_2$ on either side of the membrane. Here, the CO$_2$ transfer is 6 times faster than that of O$_2$ for equivalent membrane thickness and pressure gradient. The pressure gradient for CO$_2$ will not exceed the gradient of O$_2$ (as pump venous blood PvCO$_2$ is 45–50 mmHg and PvO$_2$ is 0). This pressure gradient and membrane thickness of 3–6 μm limits CO$_2$ transfer up to 200 ml/min/m$^2$ for most of the devices. At lower blood flow rates, the removal of CO$_2$ from the blood is more post-oxygenator effective than is the transfer of oxygen to the blood. Therefore, CO$_2$ removal can be maintained in circumstances with severe respiratory dysfunction unlike O$_2$. This has a clinical implication when ECMO is used for total gas exchange, where hypocapnea invariably results. A marked respiratory alkalosis therefore can occur, requiring the addition of 2–5% CO$_2$ during ventilation. Gas exchange is very much dependent on membrane surface area and relatively independent of blood flow rate. Any malfunction decreasing the

| Table 11: Indications for conversion from veno-venous to veno-arterial-venous or veno-arterial extracorporeal membrane oxygenation |
|-------------------------------|-----------------|
| **Inability to maintain systemic perfusion** |
| **Maximal ionotropic support with inadequate systemic pressures** |
| **Poor cardiac function on echocardiogram** |
| **High serum lactate > 8 mmol/l and persistent metabolic acidosis** |
| **Ongoing base excess ≥ -6** |
| **Deterioration of cardiac function** |

| Table 12: O$_2$ exchange (blood flow variables) |
|-----------------------------------------------|
| **Dependent on:** |
| O$_2$ concentration (driving gradient) |
| Blood flow rate |
| Blood path thickness |
| Membrane surface area |
| Membrane diffusion characteristics |
| **Independent of sweep gas flow** |

| Table 13: Comparison of lung and artificial oxygenator |
|---------------------------------|-----------------|
| **Lung** | **Oxygenator** |
| Area | 100–150 m$^2$ | 1–4 m$^2$ |
| Surface area/volume ratio | 300 | 30 |
| Diffusion distance gas/blood | 1–2 μm | 10–30 μm |
| Gas exchange both O$_2$ and CO$_2$ | 200–250 ml/min rest and 10 times increase with exercise | 200–400 ml/min maximum |

| Table 14: Factors affecting the CO$_2$ removal in a membrane lung |
|----------------------------------|-----------------|
| **Dependent factors** | **Independent factor** |
| Gas diffusion gradient across membrane | Blood flow through the device |
| Sweep gas flow rate | Membrane surface area |
membrane surface area will affect CO2 removal before it affects oxygenation. Any rise in post-membrane CO2 is a sensitive indicator of loss of functioning membrane area. Like normal lungs, oxygenator membranes are also subject to pulmonary edema, ventilation perfusion (V/Q) mismatch, pulmonary embolism, minor and major thrombosis (inlet header and distribution ports), gas embolism and hemorrhage (blood leak into gas phase). In addition, cumulating water or blood in the gas phase results in abnormalities of ventilation. This leads to full saturation of water with O2 from ventilating gas, maintaining the oxygenation of perfusing blood, whereas the CO2 clearance is selectively decreased. In this scenario, the sweep gas flow rate is selectively increased with the intention of forcing blowing the water droplets, simultaneously avoiding high pressure in the gas phase in comparison to blood phase, which leads to CO2 and H2O clearance and return the normal function of membrane. The sole advantage with artificial membrane lung is the ease and liberty to simply discard and replace the lung unit when it malfunctions, unlike the human lungs.14–18

OTHER PHYSIOLOGICAL VARIABLES PERTAINING TO TISSUE OXYGENATION ON ECMO

On ECMO, the major determinant of oxygen content is hemoglobin concentration. Appropriate blood transfusions here become the major intervention than any further intervention aiming for increment in oxygen tension beyond 100 mmHg, as the blood exiting the membrane lung is >90% saturated. Also, alkalosis and acidosis at the tissue level further impact oxygen delivery. Normal oxygen consumption is 4–6 ml/min and may be increased to 10–12 ml/min or higher in response to sepsis, hypoxia, any stimuli, hyperthermia, muscular activity, catecholamines, etc. This oxygen consumption in sick patients cannot be easily manipulated. Careful management of underlying illness, sepsis, temperature, sedation and paralysis, along with appropriate nutrition, helps in minimizing oxygen requirement on ECMO. Normal oxygen delivery is five times the oxygen consumption (giving an extraction ratio of 20%), but secondary variations in increased metabolism are normally adjusted with increase in cardiac output. The physiological critical point in tissues arises at that juncture where the oxygen delivery is reduced to just two times the consumption; till then the fall in delivery is compensated by an increased oxygen extraction. Since the mixed venous saturation (mSvO2) reflects the extraction ratio, an extraction ratio of 25–20% will correspond to mSvO2 of 75–80%. If delivery of oxygen is less than twice the oxygen consumption (extraction ratio > 50%) seen with the mSvO2 of <50%, then the oxygen supply depends on delivery. Therefore on ECMO, mSvO2 is a good surrogate marker in the management of critically ill patients. Hence, the transfusion is done with an aim to achieve a desired hemoglobin level with the adjustment of flows to achieve adequate oxygen delivery, as reflected by mSvO2 regardless of oxygen consumption. An mSvO2 of about 70% generally reflects an adequate ECMO support.19–20

DRUG DISPOSITION DURING ECMO

Even with increased application and technological advancement, information on the drug disposition is lacking during ECMO. The results of many studies on cardiopulmonary bypass are cited, but extrapolating these results onto ECMO may not be straightforward because of the differences in the duration of the two support systems. Certain characteristics of drugs may dictate whether pharmacokinetic and pharmacodynamics changes will occur during ECMO. Volume of distribution (Vd), protein binding, physico-chemical characteristics (potential for interaction with circuits), as well as physiological changes, influence of injection sites and the flow rates are among such variables. On initiation of ECMO, the rapid hemodilution that follows may result in acute changes in plasma concentrations with potentially unpredictable pharmacological effects. Evidences have also shown that significant sequestration of opioids and benzodiazepines in the components of circuit can result in higher dose requirements. Therefore, only limited conclusions may be drawn here about drug disposition. It is also important to draw a distinction between the likely effects on disposition of drugs administered prior to ECMO (bolus and continuous infusion), where the initial effects of hemodilution and protein binding changes may be greater, and those administered during ECMO where sequestration of drugs and altered hepatic and renal blood flow may play a greater role. Further studies are required not only to delineate the complex changes in drug disposition occurring during ECMO, but also to establish clear dosing guidelines. As yet, definitive dosing recommendations are only available for gentamycin and vancomycin. This same pattern of an increased volume of distribution and prolonged elimination has been found for several other drugs, including tobramycin, bumetanide and ranitidine. The benzodiazepines and propofol are largely sequestered within the circuit. Serum concentrations of heparin, morphine, fentanyl, furosemide, phenytoin and phenobarbital are also reduced by these mechanisms.
Drugs with a large Vd (e.g. fentanyl) would be expected to show only a slight change following the expansion of plasma volume, the initial lowering of plasma concentration from hemodilution being counteracted by the back diffusion of the drug into plasma from the large tissue reservoirs, since the resultant enlarged apparent Vd may affect the elimination rate of the drug. In contrast, a drug with a small Vd (e.g. gentamicin) may be significantly affected. A drug with high plasma protein binding may have a higher effective (free drug) plasma fraction (because of decreased protein binding) through heparin displacement and hence greater distribution into tissues, resulting in a higher apparent Vd. Caspofungin plasma levels are maintained during ECMO. In the case of voriconazole, it is recommended to monitor plasma levels to ensure efficacy and avoid toxicity. Hemofiltration improves outcome in ECMO patients, but it adds uncertainty to the pharmacokinetics and further complicates the determination of population pharmacokinetic parameters of drugs.\textsuperscript{[21-25]}

**Site of drug administration**

Studies suggest that drug administration distal to the reservoir may be optimal, but this site increases the risk of air embolism. Thus, many ECMO centers choose to administer drugs proximal to the reservoir, allowing the top of the venous reservoir to serve as an air trap.

**Predictors of mortality**

Level of lactate in the blood is easy to measure and is a very useful parameter that should be considered as one of the vital parameters to be checked frequently during ECMO support. Evaluation of the blood lactate levels at 24, 48 and 72 hours would help in predicting the outcome at 30 days. In addition, the rate of bleeding and the need for multiple blood transfusions during ECMO remains high, which also increases the mortality. Longer duration of ECMO support, low pH and urine output in the first 24 hours, and associated renal failure are significant factors for mortality. Exposure to high amounts of blood transfusion, extended ECMO support and sepsis increase the risk of death after successful decannulation. Further studies are necessary and advisable in the near future to provide a valid score for predicting mortality in all adult cardiac patients supported by ECMO.\textsuperscript{[26-28]}

**MORBIDITY**

**Medical morbidity**

In children, difficulty in establishing full oral feeding is common after ECMO decannulation. Feeding difficulty is reported in as many as one-third of babies, even in the presence of normal suck and swallow reflexes. Somatic growth is normal in infants who survive following ECMO. Poor growth should be evaluated for another underlying cause. Infants who survive following ECMO have a higher rate of rehospitalization for nonpulmonary and surgical conditions. The rate of sensorineural disabilities in infants who survive following ECMO averages 6% (range 2–18%) and developmental delay occurs in 9% (range 0–21%). Abnormal brainstem auditory-evoked response (BAER) with mild-to-moderate threshold elevation is seen in 25% of children following ECMO at discharge. This condition usually resolves. Sensorineural hearing loss is documented after 1 year of age in 9% (range 4–21%) of children following ECMO. Routine ophthalmic examinations during ECMO are not recommended, but are required prior to discharge in neonates having birth weight less than 2 kg. Some degree of cortical visual impairment has been seen after posterior brain injury. However, in the long term, visual function has been shown to improve. Both clinical and electroencephalographic seizure activity is reported in 20–70% of neonates on ECMO. Epilepsy is reported in 2% of patients at age 5 years. Rare neuromotor deficits range from mild hypotonia to gross motor delay and spastic quadriparesis.\textsuperscript{[29-33]}

Adult patients coming off ECMO after 2 weeks or more often have a picture of severe chronic obstructive poor CO\textsubscript{2} clearance, honeycomb appearance on CXR). This is due to V/Q mismatch which eventually resolves in a few weeks. There is a risk of deep vein especially if the femoral vein has been cannulated. It is wise to study patency of the leg veins a few days after ECMO, keeping a low threshold for an inferior some centers post ECMO in adult patients who do not receive heparin for renal replacement therapy. Once off ECMO, there is the tendency of patient dropping back into fluid overloading, anemia, hypoproteinemia, oversedation and malnutrition. Watching for this syndrome and preventing it traditionally has taken priority, as the prima motive goal for the patients weaned from ECMO is to make sure that they leave the hospital alive.\textsuperscript{[32-34]}

Psychosocial morbidity- Increased frequency of social problems, academic difficulties at school age, and higher rates of attention deficit disorder are reported in children who received ECMO. The ECMO procedure is dramatic and highly invasive. Families can feel isolated if no other patients are on ECMO in the same institution. At the age of 1 year, the stress level of the
mother of an infant previously on ECMO is the same as the stress level in the family of a preterm infant. By the age of 5 years, the family stress level is the same as that of the family of a healthy child in whom ECMO was not used.\textsuperscript{[33–39]}

**FUTURE RESEARCH AND DEVELOPMENT**

The upcoming next generation is a shift from the conventional methodology and are directed toward: 1) paracorporeal approaches (wearable devices that will be attached directly to patients); 2) intravascular approaches (respiratory catheters placed within the vena cava through a peripheral vein); and 3) intrathoracic–intra-abdominal approaches. Few of the notable developments are as follows:

**Arteriovenous carbon dioxide removal**

Principally removes CO\textsubscript{2} with some oxygenation of the blood done without any mechanical pump support. The flow rate (25–29\% of cardiac output) is much lower than ECMO and is dictated by the arterial-to-venous pressure difference of the patient and the hydraulic resistance of the artificial lung. Maximum CO\textsubscript{2} removal was approximately 100 ml/min or 96\% of total CO\textsubscript{2} production.

**Intravascular respiratory catheters**

IVOX\textsuperscript{™}, developed by Mortensen and colleagues at Cardio Pulmonics, Inc. (Salt Lake City, UT), is the only intravascular artificial lung that has undergone human clinical trials. Placed in the vena cava, it provides respiratory support at 40–60\% of the basal metabolic needs. Innovative prototypes of intravascular lung assist device (ILAD) were developed at Northwestern University, capable of O\textsubscript{2} and CO\textsubscript{2} transfer at 40–70 ml/min (20–30\% of the body’s resting metabolic needs). To enhance gas exchange, an active or dynamic (D-ILAD) form was devised, with rotation of the entire device increasing the blood convection across the fiber surfaces. This improved gas transfer performance, while providing some pumping motion to blood flow, accomplished O\textsubscript{2} and CO\textsubscript{2} transfer rates of 208 ml/min/m\textsuperscript{2} and 310 ml/min/m\textsuperscript{2}, respectively, in bovine models. Another design requiring placement through the right ventricle into the PA was developed at Penn State University as PENSIL, for Penn State Intravascular Lung. Placement within the PA maximized gas exchange. It achieved reasonable O\textsubscript{2} exchange efficiencies at 140 ml/min/m\textsuperscript{2} and CO\textsubscript{2} exchange (corrected to a blood PCO\textsubscript{2} driving force of 50 mmHg) was low, however, at only 25 ml/min/m\textsuperscript{2}. Intravascular artificial lung under research at the McGowan Institute for Regenerative Medicine in University of Pittsburgh is known as the Hattler Catheter, which was formally referred to as the intravenous membrane oxygenator (IMO). CO\textsubscript{2} removal rate achieved with the respiratory Hattler catheter tested balloon pulsation increased gas exchange by 200–300\% at the lowest blood flow rate compared to 50–100\% enhancement at the highest blood flow rate without balloon.

**Total artificial lungs**

a) In-series configuration connects proximal PA, diverting all the cardiac output through the device and returning it to the distal PA immediately upstream of the natural lungs used as an effective embolic filter. The mechanical load on the right heart increases as it provides the pumping energy for both the natural and the artificial lung. An estimated 0.11 W/(l/min) is the power used by the right ventricle. b) In-parallel configuration connects the PA and the left atrium, with only a fraction of the blood flow getting diverted. Here, the advantage is reduced right heart workload, but the disadvantage is that only a fraction of total cardiac output receives respiratory support and this fraction is not exposed to the metabolic and filtering functions of the natural lung. The power requirement of the in-parallel configuration (assuming two-thirds of total flow through the Total artificial lungs and one third through the natural lung) is roughly half that for the in-series configuration. c) The hybrid configuration attaches the inlet of the artificial lung to the proximal PA and uses a split return to the distal PA (and natural lung) and to the left atrium. This allows all the cardiac output to flow through the artificial lung with less resistance than the in-series configuration and also allows greater flow through the natural lung than the in-parallel configuration. The power requirement of the right heart for this configuration depends on the amount of blood flow through the artificial lung relative to the natural lung, and is approximately 0.08 W/(l/min). Patients with a weak or failing right ventricle would require either the in-parallel or hybrid configurations because of the reduced power required for adequate perfusion of the artificial lung and natural lung.

**Intrathoracic artificial lung**

Under development at Northwestern University, it is focused for use in acute failure to rest the lung and in chronic failure as a bridge to lung transplantation. In animal models, the average gas exchange ranged from 156 to 204 ml/min of O\textsubscript{2} and from 187 to 242 ml/min of CO\textsubscript{2}. Right ventricle required approximately 0.06 W/(l/
min) power for full blood flow through the Intrathoracic artificial lung (ITAL). The BioLung™ total artificial lung under development at MC3, Inc. (Ann Arbor, MI, USA) and the University of Michigan, is intended for complete respiratory support and as a bridge to transplant for 1–6 months. This design exhibited higher O₂ transfer efficiency to almost 300 ml/min/m², versus < 250 ml/min/m² in the old design in animal models.[40]

**Paracorporeal total artificial lung**

Chronic artificial lung (CAL): Development is under the University of Maryland for chronic lung support. As a bridge-to-transplant device, it achieves 21-day support of basal metabolic needs using rapidly rotating disk made of microporous hollow fiber membranes. The motor controller directing centrifugal disk rotation can generate pulsatile or nonpulsatile flow (reduce the impact on the right heart with its intended in-series attachment mode). The CAL generated 5 l/min flow against a 100 mmHg pressure head at 1600 rpm during steady-flow bench tests in animal models.

Integrated heart-lung assist device (IHLAD) combines the functions of a blood pump and artificial lung into one device with the goal of providing emergency percutaneous cardiopulmonary support. The IHLAD incorporates a central six-vane impeller driven by a magnetic coupling to an outer motor and is surrounded by gas-exchanging hollow fiber membranes. The blood-contacting surfaces are treated with covalently bonded heparin to reduce thrombogenicity and allow preprimed storage for emergency use.

The CORx™ system, developed by Cardiovention California, consists of a hollow fiber membrane bundle attached directly to an impeller pump. The device also includes a special technology for removing air that inadvertently enters the circuit. This compact unit has a total blood-contacting surface area of less than 1.4 m², which reduces the blood surface contact area and minimizes hemodilution of the patient. The device has been approved after clinical trials.[41]

A novel photolytic artificial lung is under development. It uses photosynthesis to convert CO₂ to O₂, obviating the need for O₂ to supply gas (as in membrane artificial lungs). The device consists of a blood pump, photolytic module of stacked cells, and a light source. In the photolytic modules, bicarbonate is protonated to form carbonic acid, which is converted to water and CO₂ in the presence of the carbonic anhydrase. The resultant water is converted to active oxygen in the presence of TiO₂ catalyst when exposed to light, and the active oxygen is converted into dissolved oxygen by the MnO₂ catalyst. Many photolytic units are integrated into a functional device to achieve the relevant rates of O₂ production and CO₂ removal.[42]

Evolution is the nature’s norm, so has been this arena with the human endeavors trying to mimic it. For ECMO, engineering and the medical fraternity had a long and consistent association in achieving this present feat and the future endeavor continues for replicating this natural physiologic system as close as possible.

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This tutorial will be followed by part II in the forthcoming issue of Annals.

- Editor

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