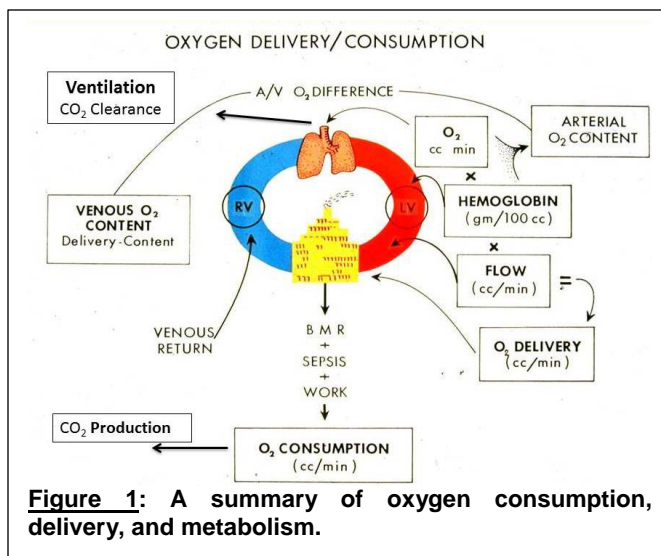


## THE PHYSIOLOGY OF EXTRACORPOREAL LIFE SUPPORT

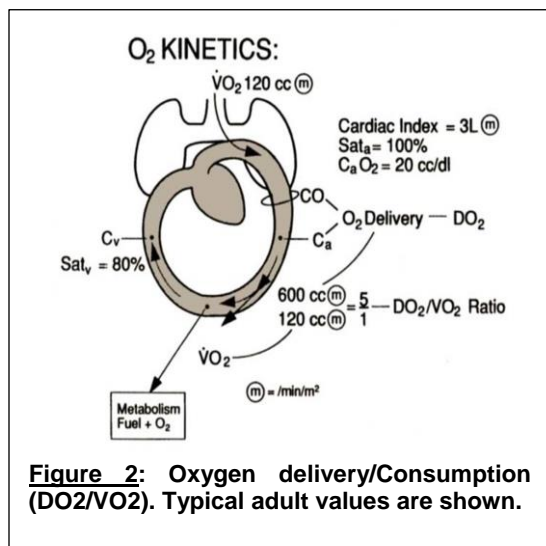
ECLS (ECMO) is the use of mechanical devices to support heart and/or lung function in severe heart or lung failure unresponsive to optimal conventional care. With circulation and respiration supported by ECMO, damaging heart and lung treatment can be stopped (vasopressors, high ventilator settings) while the failing organs are treated, recover, or can be replaced. Managing patients with ECMO is very different than conventional care and requires a thorough understanding of cardiopulmonary physiology, pathophysiology, and ECMO physiology. This chapter includes a brief review of normal and abnormal cardiopulmonary physiology, and the physiology related to mechanical replacement of circulation and respiration.

### Cardiopulmonary Physiology

The essentials of normal cardiopulmonary physiology are summarized in **Figure 1**. All the tissues of the body function by combining substrates (food) with oxygen, producing heat, energy,  $\text{CO}_2$ , and water. This process is called metabolism. **Metabolism** is measured by measuring the amount of oxygen consumed per minute, which is called  $\text{VO}_2$ . The rate of metabolism for adults at rest is  $3\text{cc/kg/min}$  or  $120\text{cc/min/m}^2$  for a typical adult (children  $4\text{cc/kg}$ , infants  $5\text{cc/kg}$ ). Metabolism is controlled by a center in the brain and increases or decreases depending on activity and other factors.



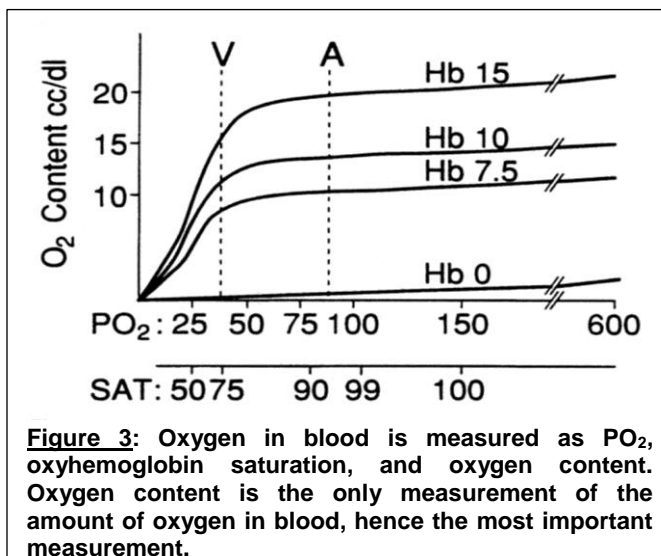
Metabolic rate increases with moderate activity, fever, drugs, and hormones. It decreases with sleep, paralysis, and cooling. Metabolic rate increases as much as five times in extreme exercise. When the metabolic rate changes, the delivery of substrate and oxygen changes in proportion, accomplished by a change in cardiac output. The amount of oxygen available for metabolism is normally five times the amount actually used by the tissues. A complex system of reflexes and hormones keeps this all in balance, referred to as homeostasis.



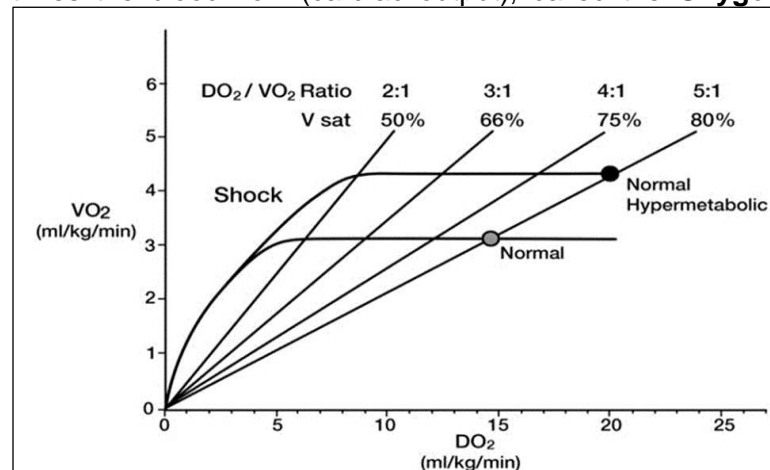
The oxygen gets into the blood through the lungs and arrives in tissues via perfusion of the capillaries. About 20% of the oxygen is removed for metabolism so 80% of the oxygen is still in the venous blood on the way back to the heart and lungs.  $\text{CO}_2$  is produced during metabolism; the amount (the  $\text{VCO}_2$ ) is essentially the same as the amount of oxygen consumed, ( $3\text{cc/kg/min}$ ). The  $\text{CO}_2$  comes out of the blood in the lungs and into the exhaled air. The amount of oxygen consumed and  $\text{CO}_2$  produced is different for each organ but the average for all organs is measured by  $\text{O}_2$  and  $\text{CO}_2$  exchange in the lungs (**Figure 2**). These principles apply to all ages

and sizes, and size-specific parameters are normalized to weight or BSA. Typical adult values are used in these examples.

**Oxygen in blood.** The **oxygen content** is the amount bound to hemoglobin plus the amount dissolved in plasma. These are measured as  $(\text{Hb gm/dL} \times \% \text{ saturation} \times 1.34 \text{ ccO}_2/\text{gm})$  and  $(\text{PO}_2 \times .003 \text{ cc/mmHg/dL})$ . Oxygen content is difficult to measure directly so is usually not reported on print outs from the blood gas machine but is the most important (perhaps the only important) measurement of oxygen in blood. In clinical practice the amount of dissolved oxygen is less than 1% of the content, so is often ignored. The relation of these three measurements is shown in **Figure 3**. Notice that there is twice as much oxygen in normal blood with an  $\text{O}_2$  content of 20cc/dL than in anemic blood with a content of 10cc/ dL, even though the saturation and  $\text{PO}_2$  are the same in both samples.



The amount of oxygen delivered to metabolizing tissue is the oxygen content in arterial blood times the blood flow (cardiac output), called the **Oxygen Delivery ( $\text{DO}_2$ )**. For an adult the normal  $\text{DO}_2$  is  $600 \text{ cc/min/m}^2$  ( $20 \text{ cc/dL} \times 300 \text{ dL/min/m}^2$ ).



For an adult the normal  $\text{DO}_2$  is  $600 \text{ cc/min/m}^2$  ( $20 \text{ cc/dL} \times 300 \text{ dL/min/m}^2$ ). The normal oxygen consumption at rest is  $120 \text{ cc/min/m}^2$ , abbreviated as  $\text{VO}_2$ . These phenomena are described in **Figure 4**. The  $\text{DO}_2$  is controlled by homeostatic mechanisms to be 5 times  $\text{VO}_2$ , so in a resting adult 20% of the available oxygen is used for metabolism, leaving 80% in the venous blood. Therefore the normal arterial oxygen of a patient breathing air is  $\text{PO}_2$  90mmHg, saturation 100%,  $\text{O}_2$  content 20cc/dL, and normal venous oxygen is  $\text{PO}_2$  40mmHg, saturation 80%,  $\text{O}_2$  content

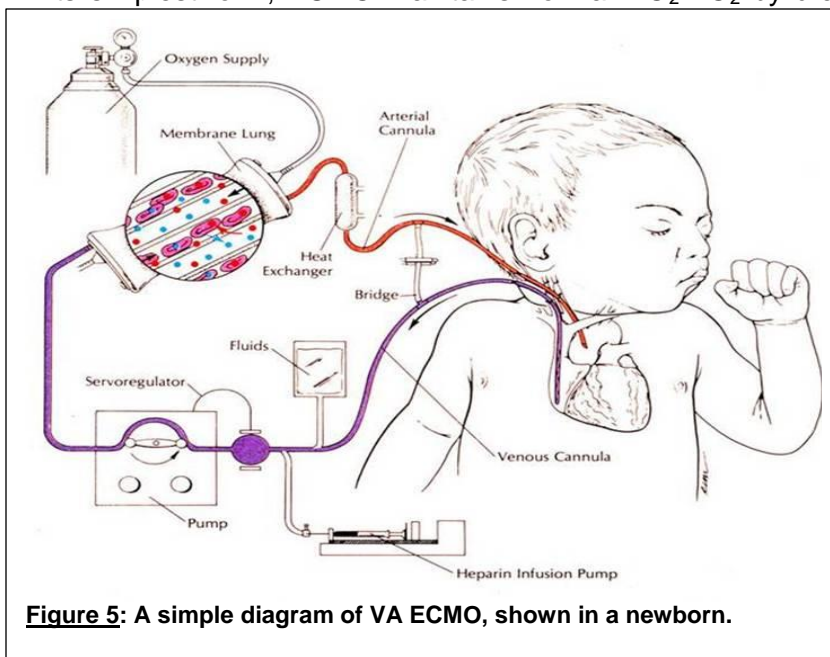
16cc/dL. The  $\text{VO}_2$  increases with exercise, catecholamines, and sepsis. The  **$\text{DO}_2$  adjusts to  $\text{VO}_2$** , maintaining the **ratio at 5:1**.  $\text{DO}_2$  is limited primarily by cardiac output. If  $\text{VO}_2$  exceeds  $\text{DO}_2$  (or if  $\text{DO}_2$  is impaired) a higher percent of the arterial oxygen content is removed in tissues, so the content in the venous blood decreases from 16cc/dL to lower levels. This is well tolerated until the  $\text{DO}_2/\text{VO}_2$  ratio is below 2:1. At that point there is not enough  $\text{O}_2$  to maintain oxygen-dependent (aerobic) metabolism and metabolism switches to anaerobic mode which causes exhaustion and lactic acidosis. The  $\text{VO}_2$  becomes dependent on the supply of  $\text{O}_2$ .

Anaerobic metabolism is tolerated for less than a few hours, leading to cardiovascular and metabolic collapse if it persists.

## Cardiopulmonary Pathophysiology

The  $\text{DO}_2/\text{VO}_2$  relationships can be affected by disease states, primarily those that affect oxygenation and cardiac output. If the  $\text{DO}_2$  is decreased compared to  $\text{VO}_2$  (in low cardiac output, anemia, or hypoxemia for example),  $\text{VO}_2$  continues at the same rate, more oxygen is extracted per dL of flow, and there is less oxygen in venous blood (as in normal physiology). Normal aerobic metabolism continues. However, when the  $\text{DO}_2$  is less than twice  $\text{VO}_2$ , oxygen supply is inadequate to maintain aerobic metabolism and anaerobic metabolism results, producing lactic acid rather than  $\text{CO}_2$ .  $\text{DO}_2:\text{VO}_2$  ratio less than 2:1 leads to supply dependency systemic acidosis, and organ failure (**Figure 4**). A goal of managing any critically ill patient is to maintain  $\text{DO}_2:\text{VO}_2$  close to normal (5:1), or at least more than the critical 2:1. So it is important to know the  $\text{VO}_2/\text{DO}_2$  when planning management.

**ECMO in cardiopulmonary pathophysiology.** ECMO is used when heart or lung failure is so severe that  $\text{DO}_2:\text{VO}_2$  is less than 2:1, or when the interventions needed to keep  $\text{DO}_2$  twice  $\text{VO}_2$  are inherently damaging (high airway pressure, high  $\text{FiO}_2$ , or vasoactive drugs at high doses). In its simplest form, ECMO maintains normal  $\text{DO}_2:\text{VO}_2$  by draining most of the venous blood,



**Figure 5:** A simple diagram of VA ECMO, shown in a newborn.

pumping it through a membrane oxygenator and into the systemic circulation. Most of the blood bypasses the heart and lungs and the artificial organs replace the function of the diseased heart and lungs. This is shown in **Figure 5**, in a neonate, as an example. On ECMO, safe  $\text{DO}_2:\text{VO}_2$  is restored and the damaging ventilator settings and drugs are discontinued. This provides time for the organ dysfunction to be diagnosed and treated, leading to organ recovery in most cases.

## The ECMO Circuit

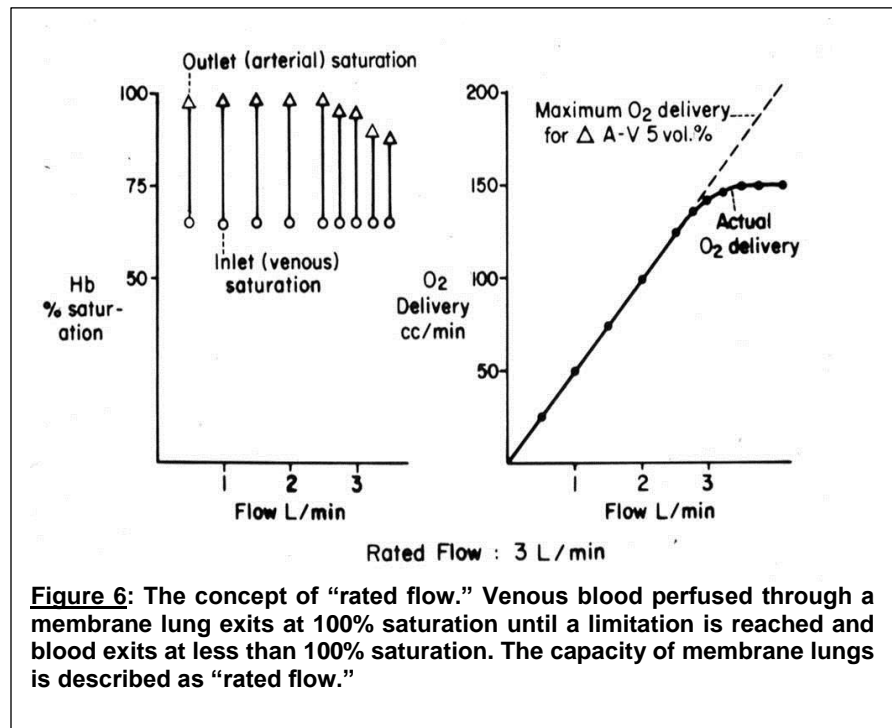
**Cannulation.** Blood flow through the extracorporeal circuit is limited by the size of the venous drainage catheter. Resistance to blood flow varies directly with the length of the catheter and inversely with the fourth power of the radius of the catheter. Consequently the shortest and largest internal diameter catheter that can be placed in the right atrium via the access vein will allow the highest rate of extracorporeal blood flow. Blood drains through the venous tubing to a pump that directs the blood through the membrane lung and back into the patient.

**Pumps.** Blood pumps are designed to direct the venous drainage through the membrane lung, then into the patient. Pumps can be centrifugal, servo-modified roller, or peristaltic. Centrifugal pumps modified for long-term use are the most commonly used. Rupture of the circuit can occur when the post-pump pressure exceeds 300mmHg, so pumps are modified to prevent overpressure. Centrifugal pumps create suction and hemolysis occurs when the suction pressure is high, so centrifugal pumps are modified to prevent high suction

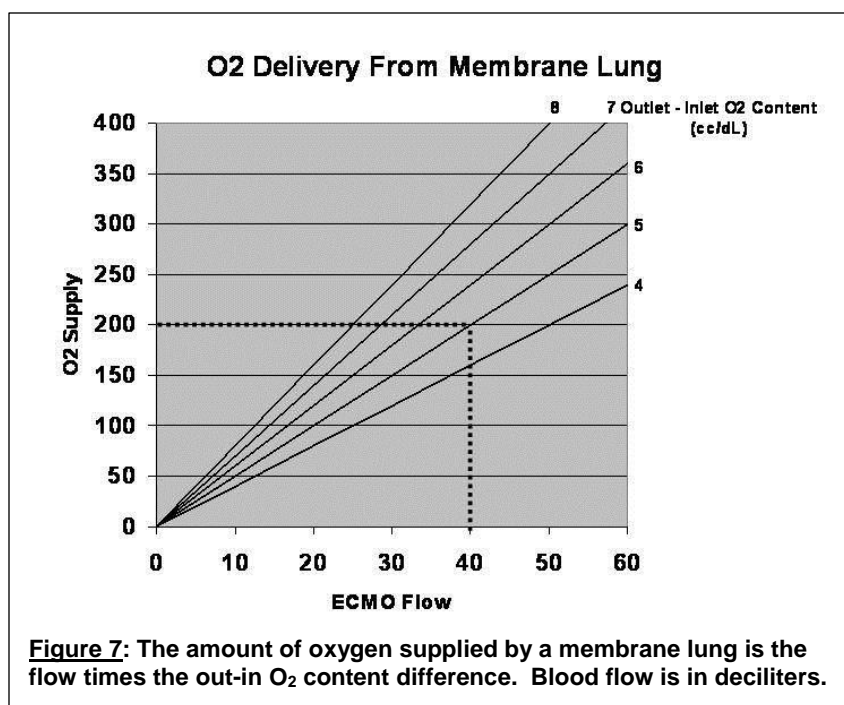
**Membrane lungs ( oxygenator).** Modern membrane lungs work by perfusing venous blood through a network of thousands of small tubes (hollow fibers). The tubes are filled with continuously flowing gas, usually 100% oxygen (the “sweep flow”). The hollow fibers are made of a material that allows gases (but not liquids) to pass through the walls of the fibers. Oxygen and CO<sub>2</sub> pass between the gas and the blood in response to the gradient between the partial pressure difference. When the gas is 100% oxygen the gradient driving gas transfer is from 600 to 40mmHg for O<sub>2</sub>, and 45 to 0 for CO<sub>2</sub>. Even though the gradient is much larger for oxygen, the solubility and diffusivity of CO<sub>2</sub> is greater, so the amount of O<sub>2</sub> and CO<sub>2</sub> exchange is roughly equal when the ratio of blood flow to gas flow is 1:1.

**Oxygen transfer in membrane lungs.** The maximal O<sub>2</sub> transfer capability of any membrane lung is determined by the gas exchange surface area and the amount of disruption of laminar flow as blood passes through the device. Laminar flow is disrupted by small secondary flows as the blood moves through the irregular blood flow path, mixing fully saturated red cells with deoxygenated red cells.

The amount of mixing by secondary flows is the most important factor in determining the maximal oxygenating capacity. All these factors are summarized in the term “rated flow.” When venous blood is perfused at a low flow through a membrane lung the hemoglobin saturation is increased to 100%, and the outlet blood is 100% saturated. As flow increases, a point is reached when the blood passes through so fast that all the red cells are not oxygenated, and the outlet saturation drops below 100% saturation. The flow of venous blood which exits the membrane lung at 95% saturation is defined as the “rated flow” (standard venous blood is defined as Hb 12gm/dL, saturation 70%) (**Figure 6**). Oxygenators for ECMO are chosen based on the rated flow for oxygenation. The size of the oxygenator is matched to the oxygen requirement of the patient.



**Figure 6:** The concept of “rated flow.” Venous blood perfused through a membrane lung exits at 100% saturation until a limitation is reached and blood exits at less than 100% saturation. The capacity of membrane lungs is described as “rated flow.”



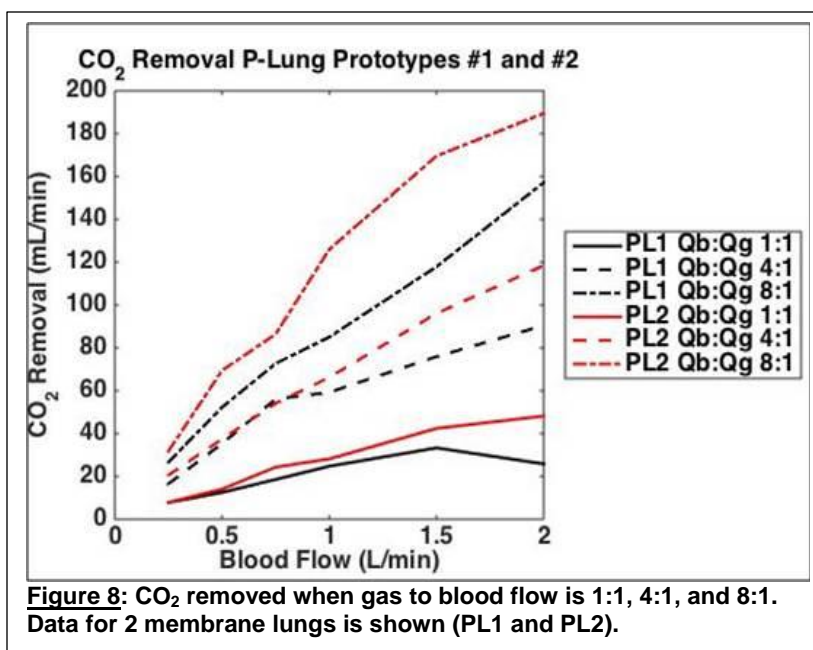
As long as a membrane lung is perfused at a rate below rated flow, the amount of oxygen delivered to the blood by any membrane lung is the outlet minus inlet O<sub>2</sub> content difference (DO-I) times the flow. Normal DO-I difference is 5cc/dL. The amount of oxygen delivered related to blood flow for different DI-O is shown in **Figure 7**.

**CO<sub>2</sub> transfer.** The amount of CO<sub>2</sub> cleared by any membrane lung is the inlet minus outlet CO<sub>2</sub> content difference (DI-OCO<sub>2</sub>). At 1:1 gas to blood flow ratio this will be about the same is oxygen. But when the

sweep to blood flow ratio is increased to as high as 8:1 a much larger DI-O can be achieved and much more CO<sub>2</sub> can be removed. Therefore when a membrane lung is used primarily for CO<sub>2</sub> removal, high gas:blood ratios are used and CO<sub>2</sub> clearance can be achieved at a much lower blood flow than when the goal is oxygenation. The sweep gas flow rate is set by the operator based on the desired PaCO<sub>2</sub>. These phenomena are demonstrated in **Figure 8**.

**Other components.** The canulas, pump, and membrane lung are connected by conduit tubing. It might seem desirable to have the circuit as close to the patient as possible, but usually the connection lines between the patient and the circuit are about 6 feet long because it is easiest to care for both the patient and the circuit when they are separated.

One reason is because the pump and lung are mounted on a bulky cart which also carries the pump motor, a large battery, a water bath for circulating warm water through the heat exchanger, an oxygen tank and gas regulator for travelling, and the monitors and displays. Monitors and alarms can include venous and arterial blood gases, pre- and post-pump pressure and flow, and blood temperature. There are access sites for infusion and blood sampling.





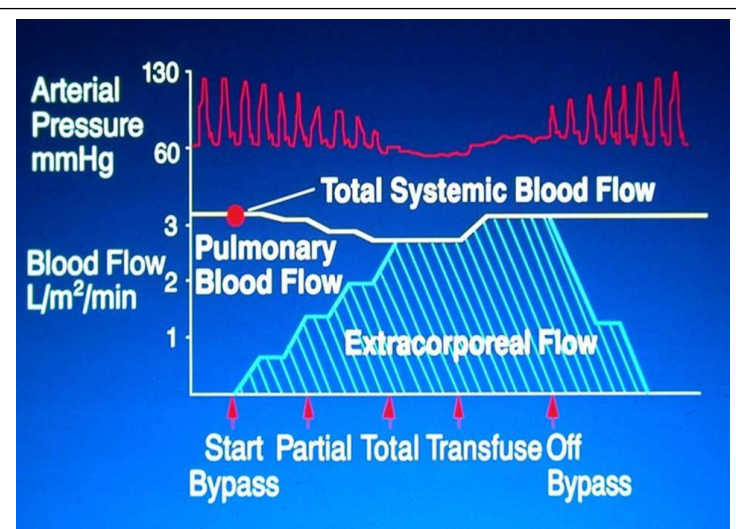
**ECMO circuit physiology.** The circuit blood and gas flow are set by the operator to match the needs of the patient. The amount of O<sub>2</sub> and CO<sub>2</sub> transfer is estimated based on all the information above, then adjusted to achieve the physiologic goals. Usually the circuit is set to totally support the circulation and respiration initially, then decreased as physiologic goals are met.

## Modes of Vascular Access and Perfusion

### Venoarterial ECMO

In venoarterial bypass (VA), the functions of both heart and lungs are replaced by artificial organs, either totally or partially. During partial VA bypass perfusate blood mixes in the aorta with left ventricular blood which has traversed the lungs. Hence, the content of oxygen and CO<sub>2</sub> in the patient's arterial blood represents a combination of blood from these two sources, and the total systemic blood flow is the sum of the extracorporeal flow plus the amount of blood passing through the heart and lungs.

**Hemodynamics.** The hemodynamics of VA access are demonstrated in **Figure 9**. As venous blood is drained from the right atrium and perfused into the aorta, the total flow remains constant but the pulse contour decreases because there is less blood ejected from the left ventricle. When the extracorporeal flow is 100% of the venous return the systemic pulse contour is flat. This is the situation in VA access for heart surgery (cardiopulmonary bypass [CPB]). In CPB the superior and inferior vena cavae are occluded proximal to the drainage cannulas so that all the venous return (except the coronary sinus) goes through the circuit. In VA ECMO the flow is maintained at about 80% of venous return, so 20% passes through the heart and lungs. The reason is to avoid stagnant flow and clotting in the pulmonary vessels and chambers of the heart (which can occur, even with systemic anticoagulation). Even in severe heart failure the heart can usually pump a small amount of blood when 80% of the circulation is provided by the ECMO circuit. In practice, this proportion of extracorporeal to cardiac flow is represented by a pulse contour of about 10mmHg. The best way to assess heart function in VA ECMO is by echocardiography.



**Figure 9:** Physiology of VA perfusion. As extracorporeal flow increases, pulmonary flow decreases and pulse pressure decreases until total extracorporeal flow is reached. During VA ECMO extracorporeal flow is ideally at 80% of total flow, so the pulse pressure is about 10mmHg.

If the heart is completely nonfunctional, all the venous return drains into the extracorporeal circuit and there is no pulse contour. The patient is on total CPB (as during cardiac surgery). This is tolerated for a few hours (enough time to operate on the heart, then restore circulation), but in ECMO this leads to two problems. First, the left side of the heart gradually fills with blood

from bronchial and thebesian venous flow. This causes increased pressure in the left ventricle, atrium, and pulmonary circulation. When that pressure reaches 20-25mmHg, pulmonary edema occurs and the LV becomes overdistended. This must be treated by draining blood from the left side of the circulation into the circuit. This is done by creating an atrial septal defect or by placing a drainage cannula in the LA (or pulmonary artery). The second problem is that blood in the cardiac chambers and pulmonary circulation will clot, even with systemic anticoagulation. This is treated by using higher levels of systemic anticoagulation and adding urgency to going from ECMO to a VAD and restoring pulmonary circulation.

**VA ECLS compared to CPB.** While the principles of gas exchange and blood flow are the same, there are several important differences between the conduct of ECLS and operating room bypass. Some of the more important differences are summarized in **Figure 10**. Because the purpose of operating room cardiopulmonary bypass is to permit operations on the heart, total venoarterial bypass is always used, with airtight occlusion of the venous drainage catheters

CPB vs ECMO*		
Major Differences	OR CPB	ECMO
Open Reservoir	Yes	No
Heparin (ACT)	>600	180
Autotransfusion	Yes	No
Arterial Filter	Yes	NO
Patient	Asleep	Awake
Environment	OR, Hours	ICU, Days
*Venoarterial bypass, same devices, physiology		
<b>Figure 10: Comparison of CPB in the operation room and VA ECMO in the ICU.</b>		

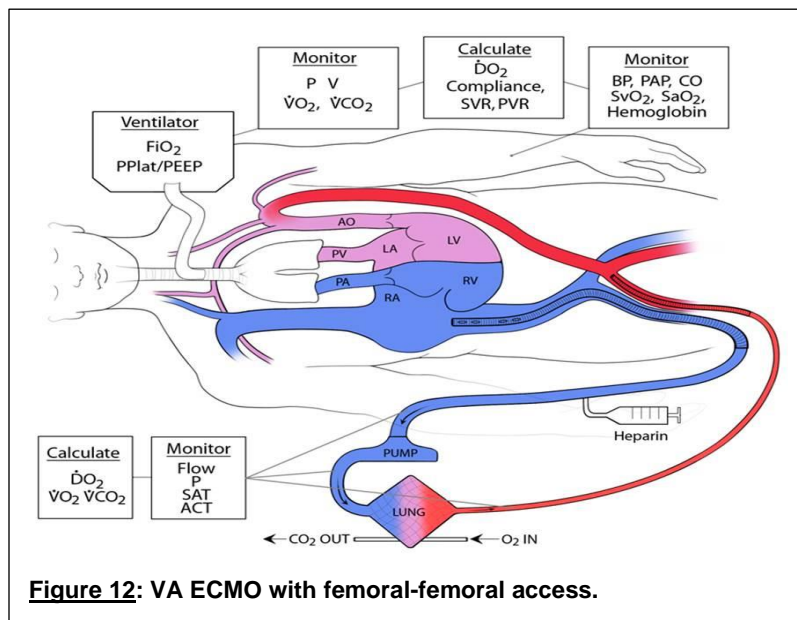
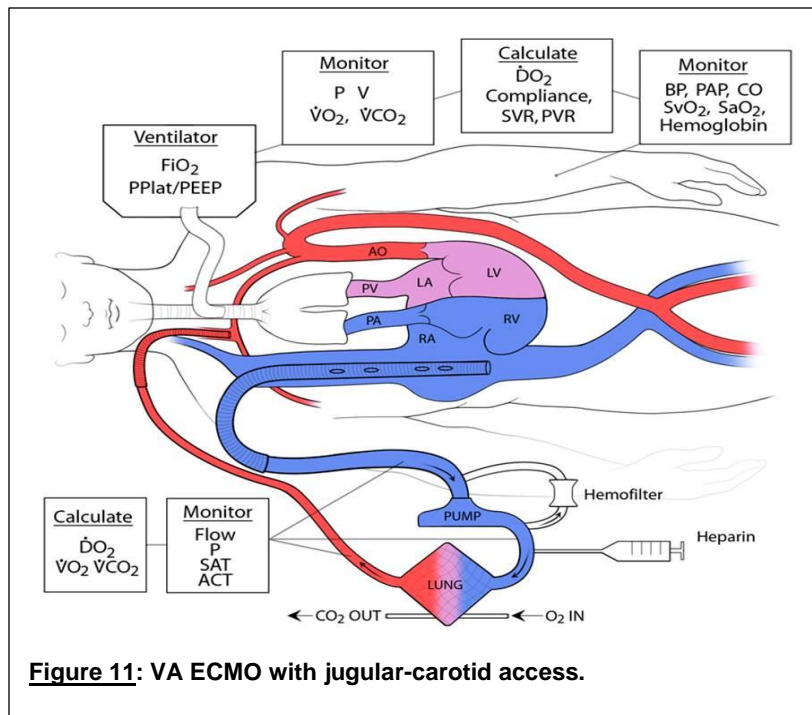
and arterial access, usually directly into the aorta. Because there is total stagnation of blood in the pulmonary circulation and some chambers of the heart, total anticoagulation is required, achieved by giving a huge dose of heparin to make the whole blood clotting time infinitely long.

This anticoagulation, and uncontrolled blood flow into the operative field from the coronary sinus, bronchial veins, and thebesian veins, results in continuous bleeding which is managed by aspiration and filtration of the shed blood with return to the venous reservoir (so called cardiomy suction or autotransfusion). To minimize this bleeding into the field, and to minimize any risks associated with high blood flow, it is common practice to manage systemic perfusion at abnormally low levels of blood flow (2-2.4L/m<sup>2</sup>/min) and abnormally low hematocrit (typically 20%). This combination of low blood flow and low hematocrit leads to very low systemic oxygen delivery, which could result in oxygen debt and metabolic acidosis except that total body hypothermia is usually implemented, maintaining the ratio of delivery to consumption in the normal range of 5:1. Therefore a very efficient heat exchanger and a large water bath are required for cardiopulmonary bypass for heart surgery.

Aside from these differences in perfusion technology, the entire approach to management of extracorporeal circulation is quite different when comparing CBP to ECLS. Cardiopulmonary bypass is conducted in the operating room with the sole intention of operating upon the heart. There is an appropriate sense of urgency to minimize the time on bypass. Complications including myocardial damage, renal failure, liver failure, hemolysis, and abnormal bleeding increase proportionate to the amount of time on bypass. Unlimited amounts of bleeding in the operating field are tolerated and managed by autotransfusion, with the realization that the effect of heparin will be reversed by protamine at the end of the procedure. An hour or two of rewarming and attempts to come off bypass is considered an exceedingly long and tedious interval. Sometimes huge doses of catecholamines are given to encourage a sluggish heart simply in order to come off bypass. If the patient cannot be weaned off bypass in a few hours, a mechanical support system (ECMO or VAD) must be instituted. The patient is anesthetized and

paralyzed and it is impossible to directly evaluate neurologic function. Everyone caring for the patient measures success or failure in hours of CPB.

In contrast, ECLS is managed in the ICU by a team expecting days or weeks of continuous care. The patient is maintained awake or awakened at regular intervals to evaluate neurologic function. Feeding, ventilation, antibiotic management, and renal function are all-important aspects of ECLS care. The use of inotropic drugs and high ventilator settings is minimal, and weaning from bypass may proceed over a period of hours or days. The patient commonly lacks heart, lung, or renal function for days, and futility is conceded only after many days of vital organ failure.



### Gas exchange in VA access.

During VA ECMO fully saturated blood from the circuit is perfused into the aorta and mixes with blood from the left ventricle. If the lungs are functioning well the mixed blood is well oxygenated and has normal  $PCO_2$ . The patient can be weaned from the ventilator and managed awake. If the lungs are functioning poorly or not at all, the systemic blood gases will reflect the mixture of the cardiac and extracorporeal flows, resulting in lower oxygenation proximal to the site of mixing. If the mixing is in the proximal aorta, blood to the brain and coronary

circulation is well oxygenated. This is demonstrated in **Figure 11**. In femoral artery access the mixing takes place in the mid aorta, so the upper body is perfused by the blood from the left ventricle. This can result in differential circulation with the lower body perfused by fully saturated red blood while the upper body is perfused with desaturated blue blood. This is referred to as the Harlequin or red feet-blue head syndrome. This is demonstrated in **Figure 12**. The management of the Harlequin syndrome is to perfuse some of the post-oxygenator blood into the right atrium (combining VA with VV perfusion). This is accomplished by inserting



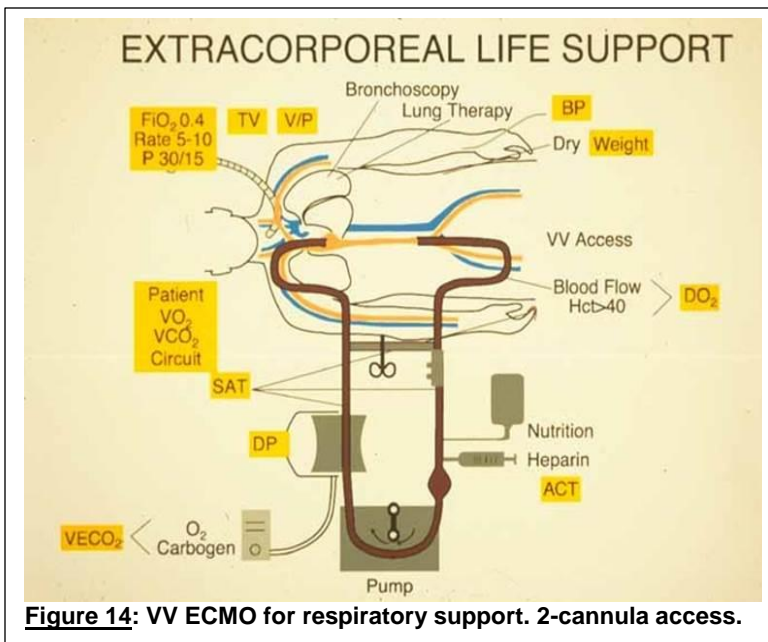
The diagram illustrates a patient undergoing VA ECMO. A ventilator is connected to the trachea, with labels for  $\text{FiO}_2$  and PPlat/PEEP. A central venous catheter is inserted into the right atrium (RA) for drainage, with a label for 'Monitor P V  $\dot{V}\text{O}_2$ ,  $\dot{V}\text{CO}_2$ '. A second catheter is inserted into the descending aorta (AO) for perfusion, with a label for 'Calculate  $\dot{V}\text{O}_2$  Compliance, SVR, PVR'. A third catheter is inserted into the ascending aorta (AO) for return of oxygenated blood to the right atrium, with a label for 'Monitor BP, PAP, CO SvO<sub>2</sub>, SaO<sub>2</sub>, Hemoglobin'. The heart is shown with its four chambers: RA, LA, LV, and RV. The pulmonary artery (PA) and pulmonary vein (PV) are also labeled. A pump is connected to the drainage catheter, and a heparin syringe is shown. The pump output goes to the lung, with labels for 'Calculate  $\dot{V}\text{O}_2$   $\dot{V}\text{O}_2$   $\dot{V}\text{CO}_2$ ' and 'Monitor Flow P SAT ACT'. The return line from the lung goes back to the RA. Arrows indicate the flow of blood:  $\text{CO}_2$  OUT and  $\text{O}_2$  IN.

**principles.** In VA access the parameters described in **Figures 9,11,12,13** are monitored and  $\text{VO}_2/\text{DO}_2$  are calculated from these measurements. That information is used to adjust the ECMO variables and the patient variables to maintain  $\text{DO}_2/\text{VO}_2$  at 3:1 or higher.

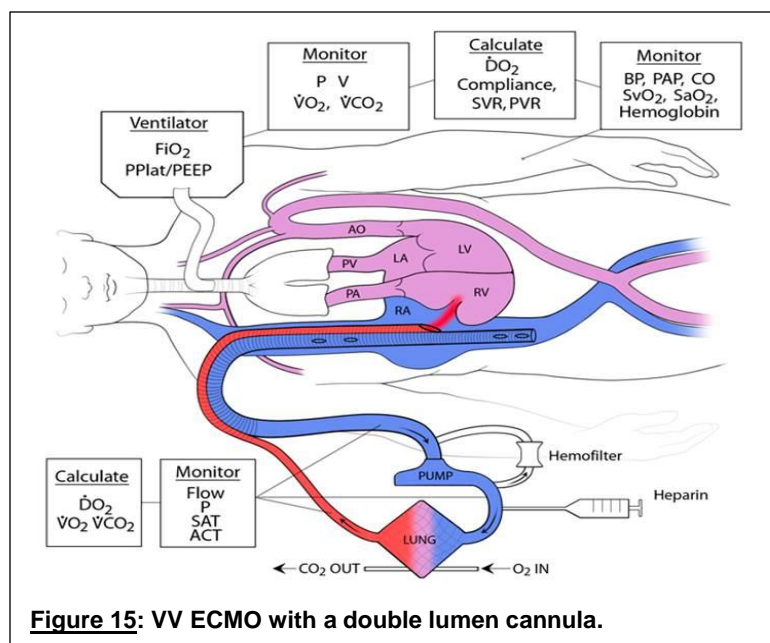
1. Plan the circuit based on the best estimation of the metabolic rate (adults, 3-4cc/kg/min for both O<sub>2</sub> and CO<sub>2</sub>) and the drainage flow which can be achieved from the largest drainage cannula which can be placed. Plan for total support, realizing that there may be some native lung function and total support may not be necessary. For a septic 80kg adult you will need 5L/min flow, and an oxygenator with rated flow over 5L/min to supply 300cc O<sub>2</sub>/min.
2. On ECMO go to the highest flow to determine the maximum drainage capacity following the pulse contour. If the drainage cannula is large enough, total bypass (nonpulsatile flow) will result. Then decrease the flow until the pulse contour is 10-15mmHg. Then decrease the vasoactive drugs to low or no levels. If there is no LV function establish left atrial drainage.
3. When the patient is stable (usually 6-12 hours) determine the variables of O<sub>2</sub> kinetics, using the formulas described above. If oxygen supply is adequate (DO<sub>2</sub>:VO<sub>2</sub> over 3) no changes are necessary. If oxygen supply is inadequate (DO<sub>2</sub>:VO<sub>2</sub> under 3) and the patient is anemic, transfuse to a higher hemoglobin (12-14 gm%). This will result in arterial saturation around 90% and venous saturation around 65% (DO<sub>2</sub>/VO= 3-4).
4. Manage the patient based on continuous venous and arterial saturation monitoring. Plot the position on **Figure 4** frequently. Calculate the variables if oxygen supply seems excessive or inadequate.
5. When the native heart begins to recover (pulse contour increases when flow is decreased) turn down the flow, keeping the venous saturation >70%. When the native heart function is adequate, conduct a trial off bypass. When heart function is satisfactory, decannulate.

## Venovenous ECMO

In venovenous ECMO (VV) the perfusate blood is returned to the venous circulation and mixes with venous blood coming from the systemic organs, raising the oxygen content and lowering  $\text{CO}_2$  content in the right atrial blood. This mixed blood passes into the right ventricle, the lungs, and into the systemic circulation. VV access is achieved by draining venous blood from the IVC via the femoral vein and re-infusing into the RA via the jugular (**Figure 14**), or by draining from the IVC and re-infusing into the RA via a separate lumen in a double lumen cannula (**Figure 15**).



**Figure 14:** VV ECMO for respiratory support. 2-cannula access.



**Figure 15:** VV ECMO with a double lumen cannula.

**Hemodynamics.** Hemodynamics during VV access are normal. Since the volume of blood removed is exactly equal to the volume of blood re-infused; there is no net effect on central venous pressure, right or left ventricle filling, or hemodynamics. The content of oxygen and  $\text{CO}_2$  in the patient's arterial blood represents that of right ventricle blood modified by any pulmonary function that might exist. The systemic blood flow is the native cardiac output and is unrelated to the extracorporeal flow.

**Gas exchange in VV ECMO.** In VV ECMO some of the systemic venous return is drained to the

ECMO system, oxygenated, and returned to the right atrium. Some of the systemic venous return goes directly to the right atrium where it mixes with the ECMO perfusate blood. The mixed blood passes through the right ventricle, native lungs, left heart, and into the systemic circulation. In severe respiratory failure the native lungs contribute little or none to gas exchange, so the arterial oxygenation and  $\text{CO}_2$  is the result of mixing the oxygenated ECMO blood with the deoxygenated native venous blood. As a result, the arterial saturation ranges from 60% to 90%, depending on the relative amount of ECMO flow, native venous flow, lung function, and cardiac output. The desaturated arterial blood results in normal systemic oxygen delivery as long as the cardiac output and hemoglobin concentration (oxygen content) are

adequate. These relationships are often confusing to ICU staff, because the usual goal of management is to keep the arterial saturation over 90%.

## Oxygenation

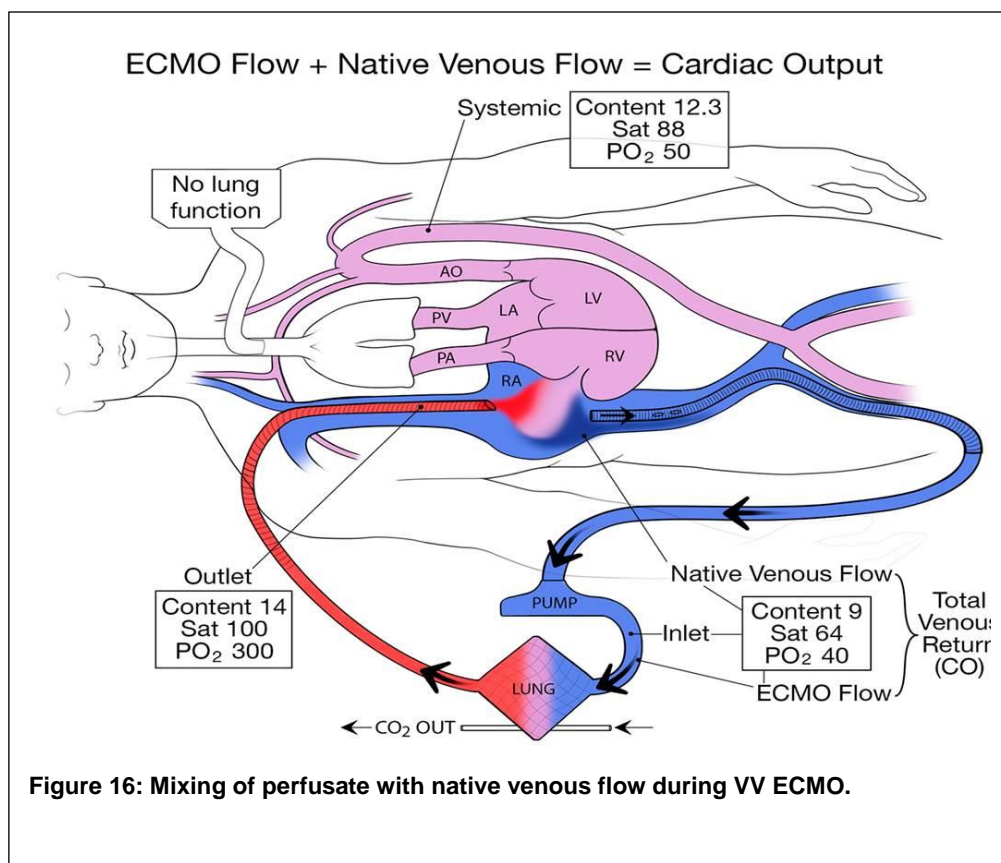
To illustrate the principles, the discussion begins with the assumption that there is no native lung gas exchange (which is often the case in ECMO patients). In a membrane lung (as in the native lung) oxygenation is a much greater problem than CO<sub>2</sub> removal, so the initial focus is on oxygenation. The circuit and blood flow are planned for total oxygen supply (VO<sub>2</sub>) at rest or during moderate exercise. For adults this is 120cc/min/m<sup>2</sup> (3cc/kg/min), or 250-300cc of oxygen/min for average adults. The membrane lung must be large enough to transfer this amount of oxygen (all devices on the market can do this, see “rated flow”). The oxygen supply from the membrane lung is dependent on the blood flow, the hemoglobin concentration, and the difference between the outlet minus inlet O<sub>2</sub> content. Because the outlet blood is typically 100% saturated and PO<sub>2</sub> is over 500mmHg the dissolved oxygen can be as much as 10% of the oxygen content.

Blood flow is limited by the resistance to flow in the drainage cannula, the suction produced by the pump or siphon, and the geometry of the cannulated vessel (usually the vena cava or right atrium). Typical maximum flow at 100cm/H<sub>2</sub>O suction for common sizes of venous cannulas is 4-5 liters per minute.

**Relation of extracorporeal oxygenation to systemic oxygen delivery.** Assuming that there is no native lung function, the systemic arterial content, saturation, and PO<sub>2</sub> will result from mixing the flow of oxygenated blood from the membrane lung with the flow of venous blood which passes into the RV, not into the ECMO drainage cannula, (hereafter referred to as the **native venous flow**). The amount of oxygen in systemic arterial blood is the result of the mixture of these two flows. These relationships are shown in **Figure 16**.

### Calculations related to mixing two flows.

When two blood flows of different oxygen contents mix, the resultant oxygen content is the average of the amount of oxygen in each of the two flows (not the average of the PO<sub>2</sub>s). The amount of oxygen contributed by each



**Figure 16: Mixing of perfusate with native venous flow during VV ECMO.**

### Mixing 2 Blood Flows of Different O<sub>2</sub> Content (C<sub>1</sub> and C<sub>2</sub>)

The resultant O<sub>2</sub> content (C<sub>3</sub>) is the sum of each content x flow divided by total flow

$$\frac{C_1 \times \text{Flow}_1}{\text{Total Flow}} + \frac{C_2 \times \text{Flow}_2}{\text{Total Flow}} = C_3$$

In VV ECMO, assuming no native lung function:

C<sub>1</sub> and F<sub>2</sub> are extracorporeal content and flow

C<sub>2</sub> and F<sub>2</sub> are the venous content and the native venous flow

The equation can be solved for cardiac output and native venous flow

$$\text{Total Flow} = \text{Flow}_1 \frac{(C_1 - C_2)}{C_3 - C_2} = \text{Cardiac Output}$$

$$\text{Flow}_2 = \text{Total Flow} - \text{Flow}_1 = \text{Native Venous Flow}$$

**Figure 17:** The relationships among flow and O<sub>2</sub> content are shown in the equation. During ECMO all the variables are known except native venous flow (F<sub>2</sub>) and total flow (cardiac output). Native venous flow can be calculated. Cardiac output is F<sub>2</sub> plus F<sub>1</sub>. This assumes no lung function and no recirculation.

### Mixing 2 Blood Flows in VV ECMO: Example 1

Using O<sub>2</sub> Content:

$$\frac{14 \times 4}{4 + F_2} + \frac{9 \times F_2}{4 \times F_2} = 12.3 \text{ cc/dL}$$

$$\text{Cardiac Output} = \frac{4(14-9)}{(12.3-9)} = 6 \text{ L/min}$$

$$\text{Native Venous Flow} = 6 - 4 = 2 \text{ L/min}$$

Using O<sub>2</sub> Saturation:

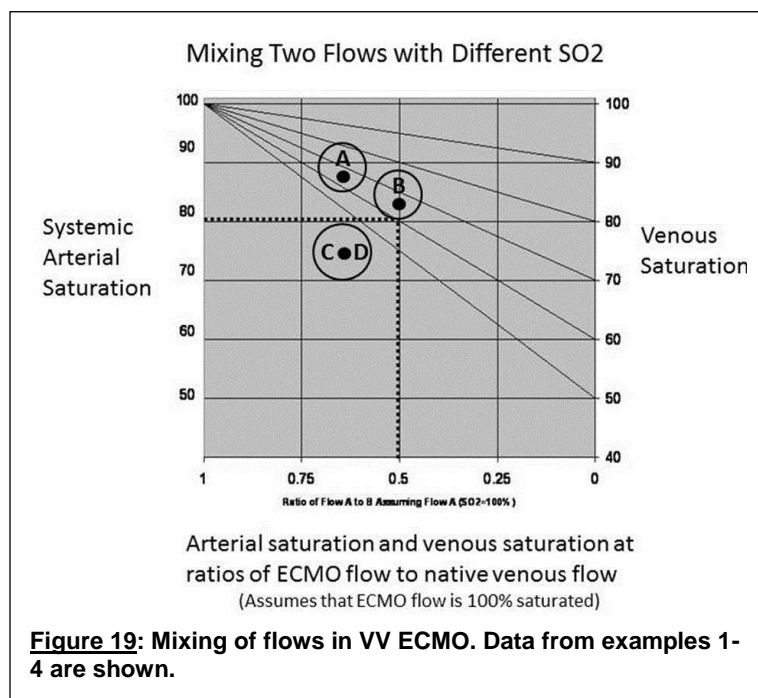
$$\frac{100 \times 4}{4 + F_2} + \frac{64 \times F_2}{4 \times F_2} = 90\%$$

$$\text{Cardiac Output} = \frac{4(100-64)}{(90-64)} = 6 \text{ L/min}$$

$$\text{Native Venous Flow} = 6 - 4 = 2 \text{ L/min}$$

**Figure 18:** The relationships among flow and O<sub>2</sub> content using the data in Example 1. The same calculations are shown using saturation rather than content.

flow is the oxygen content (in cc/dL) in the blood times the flow rate (in dL/min). The equation summarizing these events is in **Figure 17**. The same calculation can be done using saturation rather than oxygen content. This calculation using saturation is done for simplicity and is not an exact representation of the amount of oxygen content but is useful at the bedside (**Figure 18**). The combinations of flow and oxygen (expressed as saturation) variations are shown in **Figure 19**. Of the variables in the equation, all are known except the flow of venous blood which does not go through the extracorporeal circuit (the native venous flow). The native venous flow can be back-calculated from the systemic arterial oxygen content or saturation. The total venous return (cardiac output) is the sum of the native venous and circuit flow.



**Systemic arterial PO<sub>2</sub>, saturation, and content during ECMO.** Use of these equations in VV patient physiology is shown in **Figure 19**. In these examples, one variable is changed while others are held constant to illustrate the principles. Clinically, all these variables may change simultaneously and at different rates. For simplicity of the examples, we assume no native lung function, and approximate the points on the graphs. We do not account for dissolved oxygen in calculation of O<sub>2</sub> content, although it can be significant when the PO<sub>2</sub> is over 300.

**Example 1-Typical VV physiology**  
Suppose the extracorporeal flow for an adult with no lung function is



4L/min and the systemic  $PO_2$  is 50mmHg, saturation 88%,  $O_2$  content 12.3cc/dL. The Hb is 10.5gm/dL and the venous blood saturation is 64%. The patient's oxygen consumption is 200cc/min. The oxygen content of blood leaving the membrane lung is determined primarily by the concentration of hemoglobin. At hemoglobin concentration of 10.5gm/dL and 64% saturation, the drainage (inlet)  $O_2$  content is 9cc/dL and the outlet content at 100% saturation is 14cc/dL. The amount of oxygen supplied to the patient is the outlet minus inlet content (which is 5cc/dL), times the flow (40dL/min) equals 200cc oxygen supplied per minute. The native venous flow is calculated at 2L/min (per equation in **Figure 17**) so the cardiac output is 6L/min (native plus circuit venous flow).  $DO_2$  is the arterial content (12.3cc/dl) x 60dl/min = 738cc/ $O_2$ /min.  $DO_2/VO_2$  ratio is 3.64. The  $O_2$  content of native venous blood is the same as the drainage content (9cc/dL). The final complete equation is 40dL/min x 14c/dL divided by 60dL/min, plus 20dL/min x 9dL divided by 6 dL/min = 12.3cc/ $O_2$ /dL (corresponding to a  $PO_2$  of approximately 50 mm/Hg). The calculation using saturation is 4L/min x 100% + 2L/min x 70% ÷ L/min which yields a systemic arterial saturation of 88% (**Point A in Figure 19**).

**Example 2 - Increased cardiac output at fixed ECMO flow.** If, in the same patient, the cardiac output (venous return) increases to 8L/min and the circuit flow is fixed at 4L/min there will more native venous return at 64% sat mixing with the fully saturated ECMO flow. The systemic arterial content will decrease to 11.5 and the saturation will decrease to 84% corresponding to  $PO_2$  of 45mmHg. The total amount of oxygen going to the patient is the same (200cc/min), but the systemic saturation and  $PO_2$  is lower. The systemic oxygen delivery is 920cc/min. The  $DO_2/VO_2$  is 4.6. There has been a gain in systemic oxygen delivery because of the higher cardiac output, despite a decrease in arterial saturation and content. If the patient's systemic oxygen consumption is 200cc/min, systemic oxygen delivery is perfectly adequate and full aerobic metabolism is supported, even though the arterial  $PO_2$  is 45mmHg and arterial saturation is 84%. No changes are required but the ICU staff needs to understand that the hypoxemia does not require intervention. Understanding this concept can be difficult when the plan is to keep the arterial saturation over 90% (**Point B in Figure 19**).

**Example 3 – Anemia.** The patient in Example 1 is moderately anemic (Hb 10, 5 gm%) but stable. Suppose the hemoglobin suddenly drops to 8 gm%. The venous drainage is fixed at 4L/min by the resistance of the drainage cannula and cardiac output is 6L/min. The outlet content at 100% sat is 10.7. The amount of oxygen supplied by the membrane lung is 10.7 minus 9 which is 1.7cc/dl, so the membrane lung is supplying only 68cc/min. The native venous flow is 20dl/min and content is 9cc/dl. The arterial content has gone from 11.5 to 9.8, the arterial sat to 80% and the  $DO_2$  has gone from 738cc/min to 588. This results in a  $DO_2/VO_2$  ratio of 2.9 (assuming no difference in metabolic rate). However, since only 68cc of oxygen is being added per minute, and the oxygen consumption is 200cc/min, venous (inlet) content and saturation decrease quickly. When the inlet content falls to 5.7 (saturation 50%) the membrane lung O-I difference is 5cc/dl and the oxygen supplied is 200cc/min. The mixture of the fully saturated blood at 40dl/min and the 50% saturated native venous flow results in arterial saturation of 75% and arterial content 9cc/dl. The systemic oxygen delivery is 540cc/min and the  $VO_2/DO_2$  ratio is 2.7. The patient can remain in steady state with arterial saturation 75% and venous saturation 50%, but any further decrease in hemoglobin or increase in metabolic rate will result in supply dependency and lactic acidosis (**Point C in Figure 19**).

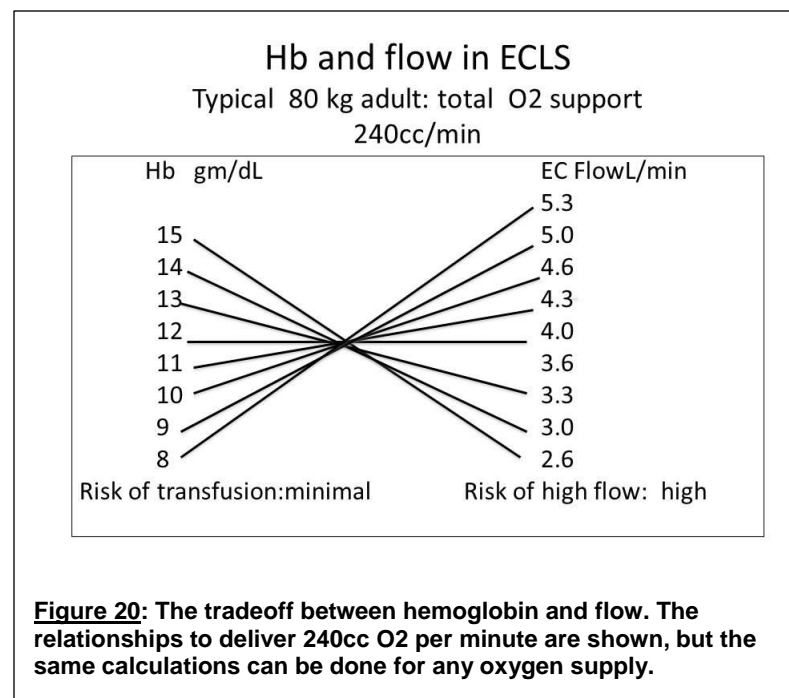
**Example 4 - Increased metabolic rate.** Suppose the patient in Example 1 becomes hypermetabolic ( $VO_2 = 250$ cc/min). The size of the venous cannula determines that the circuit flow is at maximum at 4L/min so the circuit oxygen delivery is limited to 200cc/min. The cardiac output is 6L/min. Going through the same arithmetic, the patient will fall behind at the rate of 50cc of oxygen per minute and venous content and saturation will steadily decrease (70% to

45%, for example). As venous saturation and content decrease, the oxygenator will still increase the outlet saturation to 100% and oxygen content to 14cc/dL, so the circuit outlet minus inlet oxygen difference (oxygen supply) will go up as the venous saturation goes down (from 5 to 6 for example). Systemic saturation will decrease because the saturation and content of the native venous blood going through the heart and lungs will decrease. At venous content 7.5 the O-I content difference is 6.5 and the oxygen supplied is 260cc/min. Steady state is reached with arterial saturation at about 75% and  $\text{PaO}_2$  35mmHg. The  $\text{DO}_2/\text{VO}_2$  is 2.1 and any increase in activity will lead to anaerobic metabolism which will produce lactate rather than  $\text{CO}_2$ , and lactic acidosis results. In time this will lead to multiple organ failure and death (**Point D in Figure 19**).

How can systemic oxygen delivery be increased in Examples 3 and 4? Turning up the ventilator  $\text{FiO}_2$  or airway pressure will not help. Furthermore, the whole objective is to avoid increasing  $\text{FiO}_2$  and pressure from the mechanical ventilator. There are four alternatives. The first is to increase the hemoglobin concentration to normal. When hemoglobin goes from 10.5 to 15, systemic oxygen delivery goes to 930cc/min, arterial saturation returns to 95%, venous

saturation goes to 80%, and the patient is stable and well supported. The  $\text{DO}_2/\text{VO}_2$  is 4.6. The second alternative is to increase the suction or add another cannula and increase the circuit flow from 4 to 5L/min (maintaining Hb 10.5). The  $\text{DO}_2$  increases to 792cc/min, and the  $\text{DO}_2/\text{VO}_2$  is 3.9. The third alternative for example 4 is to paralyze and cool the patient, decreasing the  $\text{VO}_2$  back to 200cc/min. A fourth is to add another membrane lung to increase the gas exchange surface, but  $\text{O}_2$  supply is still limited by the blood flow, so this will not help.

The tradeoff between extracorporeal flow and hemoglobin is



demonstrated in **Figure 20**. This example shows an 80kg man with oxygen requirement of 240cc/min, but the relationships are the same for any size patient. Under most circumstances the risks of increasing extracorporeal flow are greater than the risks of transfusion.

**Oxygenation in VV ECMO.** The combination of venous access cannula, membrane lung size, and hemoglobin concentration should be planned to match or exceed resting  $\text{VO}_2$  (120cc/m<sup>2</sup>/min for adults). The membrane lung will supply the most oxygen at a normal hemoglobin (15gm/dL). All the important variables related to blood flow and oxygenation can be measured or calculated. It is essential to know the patient's oxygen consumption and systemic oxygen delivery to decide the best way to manage the extracorporeal circuit. Hypoxemia ( $\text{PaO}_2$  40-60,  $\text{SaO}_2$  70-90) always occurs with venovenous support and is adequate to maintain normal oxygen delivery. If systemic oxygen delivery falls to a critical level (near twice consumption), circuit oxygen supply must be increased by: 1) transfusing to a higher hemoglobin or; 2) adding

additional venous drainage access to increase the flow. There is a tradeoff of risk between transfusion and increasing circuit flow which favors transfusion of RBCs. Membrane lungs function optimally at a normal hematocrit.

**CO<sub>2</sub> removal.** CO<sub>2</sub> production is equal to O<sub>2</sub> consumption (when the Respiratory Quotient is 1), so the amount of CO<sub>2</sub> exchanged per minute is essentially the same as the amount of oxygen (120cc/min/m<sup>2</sup> for adults). Because CO<sub>2</sub> is much more soluble and diffusible in blood than O<sub>2</sub>, CO<sub>2</sub> clearance will exceed oxygenation in any circumstance, so all the circuit management is based on oxygenation. If CO<sub>2</sub> clearance is the only or the major goal, much lower blood flow can be used and hemoglobin concentration is not important. The amount of CO<sub>2</sub> elimination is a function of the membrane lung surface area and the gradient between the inlet pCO<sub>2</sub> (typically 50mmHg) and the sweep gas (0). The systemic pCO<sub>2</sub> is the result of mixing circuit outlet blood (pCO<sub>2</sub> typically 30mmHg) with native flow (typically 45mmHg). Like oxygenation, the actual amount of CO<sub>2</sub> removed by the membrane lung is the inlet CO<sub>2</sub> content minus the outlet content times the flow. However CO<sub>2</sub> content is difficult to measure or calculate, so actual CO<sub>2</sub> removal is measured as the % CO<sub>2</sub> in the exhaust gas times the gas flow. Unlike oxygenation, measuring or calculating the actual amount of CO<sub>2</sub> exchanged by the circuit is not critical; the sweep gas is simply adjusted to maintain the desired systemic pCO<sub>2</sub> (typically 40mmHg)

One phenomenon unique to ECMO is the effect of water accumulation on the gas side of the membrane lung. This is the only circumstance in which CO<sub>2</sub> clearance is less than oxygenation. Understanding the reason is a good exercise in understanding how membrane lungs work.

## Arteriovenous ECMO

Arteriovenous (AV) extracorporeal circulation is commonly used for hemodialysis or hemofiltration but not for cardiac or pulmonary support. The AV route can be used for gas exchange provided the arterial blood is desaturated, and the cardiovascular system can tolerate the arteriovenous fistula with a large enough flow to achieve adequate gas exchange. This is, after all, the mechanism of gas exchange in the placenta and fetus. Because of the blood flow requirements for gas exchange support, the arteriovenous route is not a reasonable approach to total extracorporeal respiratory support, except when the patient can tolerate a large arteriovenous shunt and increase in cardiac output (such as a premature infant). However, AV flow through a membrane lung can provide CO<sub>2</sub> secretion, decreasing the need for mechanical ventilation.

## ECMO Management when the Native Lung is Recovering

All the preceding discussion describes a situation when there is no native lung function. As the native lung begins to recover, some oxygen and CO<sub>2</sub> exchange will occur. The effect will be to improve systemic arterial oxygenation and PaCO<sub>2</sub> with no change in the extracorporeal flow rate and hemoglobin. It is tempting to increase ventilator settings and FiO<sub>2</sub> in order to take advantage of this recovery, but this may add to lung injury and delay lung recovery. ECMO is continued during rest ventilator settings, and when arterial pCO<sub>2</sub> drops below 40, the sweep gas to the membrane lung can be proportionally decreased. When the systemic arterial saturation exceeds 95%, the extracorporeal flow can be gradually decreased (changing the ratio of circuit to native venous flow). When the extracorporeal support has decreased from total support to approximately 50%, extracorporeal support can be briefly discontinued (at moderate ventilator

settings) to test native lung function. When native lung function is sufficient for total patient support, ECMO can be discontinued. Because re-establishing vascular access in ECMO can be difficult, it is wise to continue ECMO support for a day or two beyond this point to allow more lung recovery, unless there is a pressing reason to take the patient off ECMO (systemic bleeding or CNS complications).

**Managing VV ECMO based on these principles.** In VV access the parameters described in **Figures 14, 15, and 16** are monitored and  $\text{VO}_2/\text{DO}_2$  are calculated from these measurements. That information is used to adjust the ECMO variables and the patient variables to maintain  $\text{DO}_2/\text{VO}_2$  at 3:1 or higher.

1. As in VA access, plan the circuit based on the best estimation of the metabolic rate (adults, 3-4cc/kg/min for both  $\text{O}_2$  and  $\text{CO}_2$ ) and the drainage flow which can be achieved from the largest drainage cannula (or cannulas) which can be placed. Plan for total support, realizing that there may be some native lung function and total support may not be necessary. For a septic 80kg adult you will need 5L/min flow, and an oxygenator with rated flow over 5L/min to supply 300cc/ $\text{O}_2$ /min.
2. On ECMO go to the highest flow to determine the maximum drainage capacity, then turn down the ventilator to rest settings ( $\text{FiO}_2$  0.3, CPAP 15-20cm  $\text{H}_2\text{O}$ ) and wean off the vasoactive drugs. The hypermetabolism will decrease to baseline. The lungs may go to total consolidation. Adjust the sweep gas to keep the  $\text{PaCO}_2$  40mm Hg.
3. When the patient is stable (usually 6-12 hours) determine the variables of  $\text{O}_2$  kinetics, using the formulas described above. If oxygen supply is adequate ( $\text{DO}_2:\text{VO}_2$  over 3) no changes are necessary. If oxygen supply is inadequate ( $\text{DO}_2:\text{VO}_2$  under 3) and the patient is anemic, transfuse to a higher hemoglobin (12-14 gm%) . If  $\text{DO}_2$  is still inadequate change the drainage cannula to a larger size and increase flow.
4. Manage the patient based on continuous venous and arterial saturation monitoring. Plot the position on **Figure 4** frequently. Calculate the variables if oxygen supply seems excessive or inadequate.
5. When the native lung begins to recover (the arterial saturation is >95%) turn down the flow, keeping the venous saturation >70%, and the sweep flow, keeping the  $\text{PaCO}_2$  at 40. When native lung function is adequate, trial off ECMO then decannulate.

## SUMMARY

Managing a patient on ECMO requires a thorough understanding of normal and abnormal cardiopulmonary physiology, and a thorough understanding the ECMO circuit. Based on this understanding, the ECMO system is used to replace part or all of heart and lung function, maintaining normal systemic physiology while the damaged organs can recover or be replaced.