Supplementary Online Content


eAppendix
eReferences
eFigure. ELSO Case and ECLS Publication Volume Trends

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix

The Physiology of Respiratory ECLS

Gas Exchange in Venovenous ECMO

Carbon dioxide removal
When providing venovenous ECMO support for a patient with respiratory failure, the device may be providing partial support to supplement the failing lungs or may even replace the gas exchange function of the lungs entirely. As with native lung gas exchange, CO₂ readily diffuses out of the blood traversing the device, and removal of CO₂ may be accomplished at relatively lower blood flow rates than what is required to oxygenate the blood. This is especially true when the partial pressure of arterial CO₂ is high, creating a stronger gradient for diffusion out of the membrane.

Oxygenation
The main limiting factor in providing adequate oxygenation is the blood flow rate through the device. The reason is that, regardless of the amount of oxygen added to the blood by the membrane lung, the oxygen saturation exiting the membrane cannot exceed 100%. Further increasing the partial pressure of oxygen in the blood leaving the membrane lung, essentially increases only the amount of dissolved oxygen, which contributes relatively little to oxygen content. The exact oxygen content will depend on hemoglobin concentration, oxygen saturation (which should be near 100%, unless the membrane lung is not functioning optimally) and the amount of dissolved oxygen. When the well-saturated blood is reinfused into the patient, it encounters “native” venous deoxygenated blood returning to the heart. As the two streams mix, the essentially fully oxygenated blood coming from the device will combine with mixed venous “native” desaturated blood. The systemic oxygenation will depend on the ratio of the oxygen content delivered by these two sources. If the blood flowing from the extracorporeal circuit is a small fraction of the overall cardiac output, then the reinfused oxygenated blood will be overwhelmed by native deoxygenated blood and the impact on systemic oxygenation will be minimal. The key point is that it is the extracorporeal blood flow-to-systemic blood flow ratio (Qₑ:Qₛ) that determines oxygenation and a ratio of 0.6 or higher typically yields an arterial oxygen saturation of at least 90%. It is important to note that this ratio is highly dynamic and dependent on the patient’s cardiac output from moment to moment, just as it is dependent on changes made to the speed of the ECMO pump. If a patient becomes agitated or develops sepsis, for instance, and the cardiac output increases, the Qₑ:Qₛ ratio will decrease and, along with it, the arterial oxygen saturation. This is a key physiologic principle of venovenous ECMO. Venoarterial ECMO is more complex in this regard.

Typical venovenous ECMO blood flow rates range from 3-7 liters per minute. The amount of flow is determined by the speed of the ECMO pump (in rotations per minute) and limited by the size of the cannulae used. To withdraw blood from the patient requires negative drainage pressures. As this pressure becomes more negative, there is a greater potential for hemolysis. Because the positive pressures generated when reinfusing blood are less prone to creating hemolysis, the size of the drainage cannula is typically the limiting factor for the rate of blood flow that is possible while minimizing the potential for hemolysis. Another factor in determining the ability of the device to provide oxygenation is the degree of recirculation. A portion of the reinfused, oxygenated blood entering the right atrium may be inadvertently withdrawn back into the circuit due to the negative pressure within the venous drainage cannula; this is known as recirculation. The proportion of blood that is recirculating is not contributing to systemic oxygenation and thereby decreases the effective blood flow rate through the circuit. Attempts to minimize recirculation by, for instance, lowering the speed of the blood pump so as to decrease the negative pressure, drawing less reinfused blood back into the circuit; or by manipulating the position of the cannula, may be crucial in providing effective oxygenation to the patient. Other factors that may affect oxygenation include the size and functioning of the membrane lung, the set fraction of delivered oxygen from the device (FDO₂), the contribution of the native lung to gas exchange, and the patient’s metabolic rate.

© 2019 American Medical Association. All rights reserved.
What is ECCO²R?
ECMO utilizes high blood flow rates and requires relatively large membrane lungs to oxygenate blood and remove CO₂. Using an ECMO device at high blood flows, one could opt to decrease the FDO₂ to 21% such that the degree of oxygenation from the device is relatively lower, yet CO₂ removal would remain high. In other words, oxygenation can be virtually divorced from decarboxylation at high blood flow rates. Conversely, at lower and lower blood flow rates, the contribution to oxygenation begins to wane (lower Qₑ:Qₛ) and oxygenation is very sensitive to changes in blood flow rate. Whereas CO₂ removal is impervious to changes in blood flow rate at the range typically used in ECMO (3-7 liters per minute) and only begins to drop off at blood flow rates below this range. Putting numbers to these rates is complex because the rate of CO₂ removal varies according to the PCO₂ entering the membrane lung, the size and efficiency of the membrane lung, and the sweep gas flow rate. Typical extracorporeal blood flow rates used when the goal is primarily CO₂ removal range from 200-1500 ml/min, and devices which can provide only this range of blood flows are thought of as ECCO²R (not ECMO) devices. These devices may also frequently use smaller membrane lungs than are used in ECMO. However, since CO₂ removal may likewise be accomplished at high blood flow rates, it is not the blood flow rate that defines ECCO²R, and neither is it the size of the cannula used (often referred to as a "catheter" when smaller sizes are used for lower blood flow rates with ECCO²R). ECCO²R is primarily defined by the intention of the clinician. It’s more a matter of the physiologic goal of extracorporeal support. If initiating support for hypercapnic respiratory failure without substantial need for extracorporeal oxygenation, for instance, or for moderate ARDS only to decrease the PaCO₂, without an intention to provide significant oxygenation, then the clinician is providing ECCO₂R.

Venoarterial ECMO in the Context of Mechanical Circulatory Support

Short-term Mechanical Circulatory Support for cardiogenic shock
Temporary circulatory support (TCS) with short-term mechanical circulatory support (MCS) devices, which includes venoarterial ECMO, has become the cornerstone of the management of patients with severe or refractory cardiogenic shock, although their use only received a Class IIb recommendation from the European Society of Cardiology. Accepted medical indications for MCS may be classified as follows: acute myocardial infarction complicated by cardiogenic shock, acute decompensated heart failure with refractory cardiogenic shock, post-cardiac surgery cardiogenic shock, fulminant myocarditis, cardiotoxic drug intoxication, stress-induced cardiomyopathy, cardiac arrest (extracorporeal cardiopulmonary resuscitation, known as ECR), post-cardiac arrest resuscitation syndrome, decompensated pulmonary vascular disease, or massive pulmonary embolism. Many of these patients receive a device as salvage therapy after having already developed signs of refractory cardiogenic shock with multi-organ failure. In these situations, mechanical assistance is used as a bridge to decision-making if the patient survives the first days of support. In patients with potentially reversible etiologies of heart failure (e.g. myocarditis, myocardial stunning post-myocardial infarction), a short-term device may also be used as a bridge to cardiac function recovery. Earlier intervention with MCS devices, prior to the onset of multi-organ failure is preferred.

The use of the intra-aortic balloon pump (IABP), which had been the only MCS device widely available for almost five decades, has markedly decreased recently following the publication of the IABP-SHOCK II trial. In this study conducted in patients with cardiogenic shock complicating acute myocardial infarction, there was no difference in 30-day mortality between patients randomized to IABP versus conventional treatment. The utility of IABP in other cardiogenic shock populations remains unclear.

In the last decade, venoarterial ECMO has been increasingly used for cardiogenic shock since it provides both respiratory and cardiac support, is easy to insert at the bedside using percutaneous peripheral vascular cannulation, provides stable flow rates, and is associated with less organ failure after implantation compared to large biventricular assist-devices that require open-heart surgery. Other short-term MCS devices include short-term ventricular assist devices (VADs), such as the Impella (ABIOMED Inc., Danvers, MA, USA), a catheter-based axial pump positioned in a retrograde fashion across the aortic valve into the left ventricle, and the TandemHeart (LivaNova, London, UK), an extracorporeal centrifugal pump which drains blood from the left atrium using a trans-septal approach, that is, a cannula introduced via the femoral vein and extending across the inter-atrial septum, pumping the blood back into the femoral
artery. Compared to venoarterial ECMO, these systems are more expensive, do not provide respiratory support and are not easily adapted to patients with severe biventricular failure. Long-term VAD support and total artificial heart devices are also available for support outside the ICU or hospital.

**Venoarterial ECMO: the Basics**

The use of venoarterial ECMO in adults is also growing rapidly, including when used as extracorporeal cardiopulmonary resuscitation, known as ECPR (eFigure, A). Venoarterial ECMO is typically achieved with a femoral venous drainage cannula and a return cannula in the contralateral or ipsilateral femoral artery (although several other configurations may be used). In this configuration, the oxygenated reinfused blood travels retrograde up the aorta toward the heart. When there is little or no native cardiac function, the retrograde reinfused blood reaches the aortic arch and perfuses all the organs of the body along the way. If, however, there is a degree of native cardiac function (or native function is recovering), then the retrograde flow competes directly with this native flow and the degree to which the reinfused blood extends up the aorta depends on the relative force of the two competing streams of blood.

**Competitive Flow in Venoarterial ECMO**

This competitive flow in peripheral venoarterial ECMO results in a mixing point, the point at which the two flows meet. The mixing point itself is quite dynamic, varying with the relative strength of the native cardiac and ECMO flows as well as the distribution of systemic vascular resistance. Native flow depends on cardiac contractility, pre-load (which is lowered by the act of draining blood into the ECMO circuit and reinfusing it directly into the arterial circulation), and afterload, which is increased by directing a jet of blood back toward the aortic valve. Medications (e.g. inotropes) and the addition of other mechanical circulatory support (MCS) devices may modulate the native cardiac flow. The ECMO blood flow is, of course, dependent on the amount of blood drained and reinfused and may be modulated by the pump (and limited by the size of the cannulae, especially the drainage cannula).

The concept of competitive flow is important for understanding the afterload imposed on a failing or recovering heart with venoarterial ECMO. When the heart is weak or non-functioning, it explains how the unopposed ECMO blood flow can shut the aortic valve resulting in stasis and potentially clot formation within the left ventricle or other cardiac chambers (a devastating complication). However, the concept takes on added significance when native gas exchange through the patient's lungs is compromised sufficiently such that native cardiac output is deoxygenated. This may occur if there is intrinsic lung disease or if the added afterload results in frank pulmonary edema, for instance. In such a case, residual native cardiac output delivers deoxygenated blood to the mixing point and, most importantly, will include the coronary and carotid arteries if the mixing point is far enough from the heart, resulting in poor oxygen delivery to the heart and brain, respectively, despite the delivery of oxygenated blood from the ECMO device into the aorta on the other side of the mixing point. This split in oxygenation between the upper and lower circulations has been termed differential hypoxia and the Harlequin Syndrome, among other terms.

Competitive flow is not eliminated by reinfusion into an axillary, subclavian or innominate artery. Reinfusing in a physiologic direction by directing blood into a cardiac chamber, such as the left atrium, or to the proximal aorta, will effectively eliminate this issue.

**The Convergence of Venovenous and Venoarterial ECMO**

Numerous other more complex configurations exist to support a wide range of physiologic needs. Venovenous-arterial ECMO, for instance, drains venous blood in the same fashion as venovenous ECMO, but splits the reinfused blood, sending it into two separate cannulae connected by a Y-connector, so that a portion of the blood enters the arterial system to provide circulatory (mean arterial blood pressure) support and the remainder enters the venous system through a separate cannula to provide a degree of pulmonary (oxygenation and ventilation) support, if both are needed. Venovenous-arterial ECMO is another strategy to overcome the issue of competitive flow when native lung gas exchange is sufficiently impaired.

**Venting the Left Ventricle**

The afterload imposed on the left ventricle by retrograde venoarterial ECMO blood flow may result in increased left ventricle pressures, left ventricular distension and frank pulmonary edema. It may increase myocardial oxygen demand and, as previously mentioned, it can close the aortic valve. Unloading the left ventricle, known as venting, in patients at risk for such complications, is of paramount importance in affected patients. The first strategy should aim at decreasing left ventricular afterload by decreasing the
ECMO blood flow and promoting left ventricular ejection with or without inotropes. Combining an IABP with venoarterial ECMO, which decreases afterload when it deflates, has also been shown to decrease left ventricular pressures and associated pulmonary edema.\textsuperscript{18-21} Direct venting of left-sided cardiac chambers or the pulmonary artery is a more common means of venting than, for instance, percutaneous balloon atrial septostomy to open a left-to-right atrial shunt. Perhaps the most potent form of venting may be accomplished with the use of a second MCS device in conjunction with venoarterial ECMO, in particular the Impella.\textsuperscript{22,23}
eReferences


eFigure A: Extracorporeal life support (ECLS) case volume trends: 1987-2017

Data obtained from Extracorporeal Life Support Organization (ELSO) International Summary, January 2019. Trends are shown for all cases of ECLS in the registry by year (blue line), including adult, pediatric and neonatal age groups and all respiratory, cardiac and ECPR cases; all adult ECLS cases (orange line), including respiratory, cardiac and ECPR; all pediatric ECLS cases (grey line); all neonatal ECLS cases (yellow line); and a breakdown of adult cases into respiratory (light blue), cardiac (green) and ECPR (dark blue). Data collection for the registry is best characterized since 1987. Data reflect those cases voluntarily entered into the ELSO registry by member centers and do not represent all cases performed worldwide. An inflection point is noted soon after 2009, with subsequent volume rising most rapidly for adult respiratory and cardiac ECLS, with less pronounced increases in adult ECPR and in pediatric ECLS, whereas neonatal ECLS volume remained stable during this period of time. Because the International Summary in January 2019 was incomplete for 2018 cases, 2018 is not included. However, the overall trend for 2018 continues to show an increase in the use of ECLS.
eFigure B: Number of extracorporeal life support (ECLS) publications by year: 1960-2018

Number of publications regarding ECLS, by year, for all indications and all age groups. Derived by searching PubMed, according to the following search terms: extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, extracorporeal life support, extracorporeal cardiopulmonary resuscitation, ECMO, ECCO$_2$R, ECLS and ECPR. Search terms were each separated by "OR". PubMed Publication Dates Custom search was used, by year (January 1$^{st}$ through December 31$^{st}$ of each year) 1960 through 2018. Search date January 27, 2019.