Literature Review – The Evidence for ECCO$_2$R

The idea of using cardio-pulmonary bypass (CPB) systems for longer term support of acute respiratory failure was first attempted in adults by Hill et al in 1972. Like its CPB predecessor, this early form of extracorporeal support involved high flows with veno-arterial cannulation. The primary goal and challenge was to replace the full oxygenation performance of the lungs so they could be rested and allowed to heal, hence the term extracorporeal membrane oxygenation, or ECMO, evolved. Although this term is often used today as a general term for any mode of extracorporeal gas exchange, it is in fact a misnomer when used to embody extracorporeal respiratory support aimed primarily at supporting the CO$_2$ removal function of the lungs.

The concept of extracorporeal carbon dioxide removal (ECCO$_2$R) evolved in response to early trials of ECMO where the high incidence of adverse events and mechanical complications relegated the therapy to only the sickest of patients as a last ditch effort. Furthermore, the high cost and complexity of the ECMO systems limited their use to a small number of high volume specialized medical facilities. As experience increased with the methods of life support for patients suffering from acute lung failure, including both mechanical ventilation and ECMO, it was soon recognized that a significant portion of gas exchange could be achieved through the native lungs using less damaging control algorithms for mechanical ventilation, and that in many cases, extracorporeal gas exchange was needed more for the partial support of CO$_2$ removal than for oxygenation. As the understanding of the underlying physiology governing gas exchange in artificial membrane lungs evolved, it was also recognized that clinically meaningful levels of CO$_2$ exchange could be achieved at much lower flows than for oxygenation, due to steep slope in the CO$_2$ dissociation curve in the physiologic range of concentrations in which CO$_2$ removal occurs (see attachment for further explanation).

The feasibility of ECCO$_2$R became evident when it was shown that oxygenation could be achieved with the lungs without ventilation (i.e. forced inspiration and expiration), by applying high O$_2$ concentrations and a continuous positive pressure. Of course, applying this form of “apneic” oxygenation results in the immediate retention of CO$_2$ and severe acidosis. However, if CO$_2$ removal could be achieved with an extracorporeal gas exchanger using safer modes of operation, the lungs could be controlled using gentler conditions to exclusively provide oxygenation, hence disassociating oxygenation and CO$_2$ removal. This concept was first developed and explored by Ted Kolobow and Luciano Gattinoni in 1977-78 through a series of in-vivo and human clinical studies which validated its feasibility.

In 1994, Morris et al published the results of a randomized control study of full ECCO$_2$R versus conventional mechanical ventilation for the treatment of severe ARDS. Survival in the ECCO$_2$R group was 33% versus 42% for the control group, which was not different statistically, but in conclusion, ECCO$_2$R was not recommended as a therapy for ARDS. However, this early trial of ECCO$_2$R still depended on multiple gas exchangers with high flow resistances and large surface areas (3.5 m$^2$), as well as the use of occlusive roller pumps, which likely contributed to the disappointing clinical trial outcomes. The exposure of blood to such large fiber surface areas required high levels of anticoagulation which resulted in significant bleeding and high blood product requirements. Furthermore, the investigators used a variant of apneic oxygenation for mechanical ventilation support (low frequency positive pressure ventilation) in conjunction to ECCO$_2$R which utilized peek pressures and tidal volumes higher than what is currently used with ECCO$_2$R to minimize ventilator induced lung injury.
The approach of “partial” CO₂ removal (PECOR) was first explored by Gattinoni et al, and published in 1986. This was an important paper because it showed that if extracorporeal support was used to provide removal of only 33% estimated basal CO₂ production in patients maintained with non-invasive ventilation (NIV), significant drops in tidal volume could be achieved with relatively small decreases in PaCO₂. This method was further explored and validated in a case study reported by Pesenti et al in 1990 of a patient suffering from bilateral bullous emphysema with recurrent pneumothoraces, bilateral air leaks and pulmonary infection, who had been on mechanical ventilation for 28 days. Partial ECCO₂R was used to allow the complete removal of mechanical ventilatory support to non-invasive ventilation, first with pressure support, then to CPAP (continuous positive airway pressure). Even though the extracorporeal system relied on large gas exchangers and a fairly complicated circuit, therapy was provided at a blood flow rate of only 0.4-0.6 L/min using veno-venous cannulation with small 12 Fr catheters. The rate of CO₂ removal was measured to be 33-71.5 mL/min which was estimated to be 22%-40% of the patient’s CO₂ production. The remainder of gas exchange occurred through the lungs using non-invasive ventilation. After 8 days, the extracorporeal circuit was able to be removed, and eventually all forms of respiratory support were suspended and the patient was ultimately discharged to home.

Partial ECCO₂R has over time become synonymous with “safe ECMO”. Originally, reduction of the risks associated with ECMO was approached by utilizing lower blood flow rates through the circuit and using veno-venous cannulation as opposed to the traditional veno-arterial cannulation. Arterial cannulation increases the risks of extracorporeal circulation because of the higher pressures that needed to be generated by the circuit pump which could cause leaks or ruptures and greater levels of hemolysis. It also increased the risks associated with potential air embolism or thromboembolism being released directly into the central arterial blood flow compared to the venous flow. As the technology and understanding of extracorporeal gas exchange has improved, further reductions in the incidence of adverse events and mechanical failures have been achieved by:

- Advances in hollow fiber membrane technology, in terms of reductions in the overall fiber diameter and wall thickness, and in prevention of plasma leakage which significantly reduces the need for gas exchanger change-outs.
- More sophisticated arrangements of hollow fiber membranes, which reduce priming volume, reduce flow resistance (pressure drop across the device), and which improve the gas exchange efficiency allowing for reduced fiber surface area and/or flow rate;
- The use of centrifugal pumps or non-occlusive pressure controlled roller pumps, which reduces damage to the blood (hemolysis) and the incidence of circuit rupture;
- Biocompatible coatings on the fibers and circuit components (typically heparin), which reduce the risk of clot formation as well as the necessary levels of systemic anticoagulation;
- The use of single dual-lumen catheters and percutaneous venous cannulation, which reduces the incidence of cannulation-associated adverse events as well as the level of patient discomfort;
- Simplifications in the system design to reduce risk of mechanical failure and operator error.

Simultaneously to the evolution of ECCO₂R technology, substantial progress has been made in the use of invasive and non-invasive ventilators to minimize ventilation induced lung injury (VILI). This
progress has lead to standard protocols of care for both acute respiratory distress syndrome (ARDS) and for acute exacerbations of COPD. ARDSNet is a clinical network that was established in 1994 by the National Heart, Lung and Blood Institute of the U.S. National Institutes of Health to carry out clinical trials of ARDS treatments. Based on a seminal randomized trial completed in 1999, ARDSNet has established a protocol for the application of lung-protective ventilation strategies which involves systematic minimization of tidal volume to < 6 mL/kg and plateau pressure to less than 30 cmH2O. A primary barrier to the successful application of lung-protective ventilation strategies is inadequate ventilation of CO2 with concomitant hypercapnia and acidosis.

For patients with chronic COPD experiencing acute exacerbations, randomized trials conducted in the early 1990s established non-invasive positive pressure ventilation methods which reduced the incidence of intubation and mechanical ventilation. However, the use of non-invasive ventilation has become the standard of care in severe exacerbations of COPD, however 26%-54% of patients with acute exacerbations fail NIV support and require invasive mechanical ventilation. Because of expiratory flow limitation in COPD, lung protective ventilation and low tidal volume strategies can be more difficult to manage. Furthermore, such patients can be difficult to wean off of mechanical ventilation due to muscle atrophy, leading to further lung impairment. The prognosis for COPD patients requiring IMV is poor, with hospital survival ranging from only 31% to 76%. The primary reason for failure of NIV is hypercapnia and severe acidosis, i.e. the inability to ventilate CO2.

To date there have been no randomized trials of current low-flow ECCO2R devices with indications for the partial support of acute respiratory failure. However, there is substantial literature support in the form of case series, retrospective analyses and prospective non-randomized studies. The most well studied device is the Novalung interventional lung assist (iLA) device, which is a simple pumpless extracorporeal therapy which utilizes arterial pressure to drive blood flow through a hollow fiber membrane cartridge at flows between 0.5-4.5 L/min using femoral artery to femoral vein cannulation. The Novalung has been shown to provide clinically beneficial levels of CO2 removal not only in allowing for lung protective ventilation strategies in ARDS patients, but also in acute hypercapnic respiratory failure of life-threatening asthma and for bridge to lung transplantation. The simplicity and efficacy of the Novalung has garnered renewed interest in ECCO2R, however control of blood flow is limited and may require concomitant use of norepinephrine to maintain the pressure gradient between arterial and venous blood. A further drawback of this system is tied to its femoral arterial access which has been associated in 12% to 25% of patients with serious complications, including limb ischemia, compartment syndrome, and amputation.

There are several literature publications which demonstrate benefit in using the iLA for ECCO2R to provide partial support to allow for the application of lung-protective ventilatory strategies. In 2009, Zimmermann et al published a prospective pilot study of 51 patients meeting ARDS criteria who were treated with the iLA to test the hypothesis that timely initiation of ECCO2R “using clear algorithms and an improved cannulation technique will positively influence complication rates and management of lung protective ventilation.” Initiation of the iLA demonstrated marked improvement in PaCO2 allowing rapid reduction in tidal volume to ≤ 6 ml/kg and in plateau pressure. The algorithm introduced in this report for identifying patients that would benefit from ECCO2R stipulated the insertion of iLA mainly for ECCO2R purposes facilitating lung-protective ventilation in acute lung injury or early ARDS. This algorithm demonstrated a trend for improved mortality compared to an earlier study by Bein et al where
the iLA device was initiated in life threatening rescue situations with well established ARDS. In this study, 90 patients with severe ARDS were treated with mechanical ventilation and the iLA. The main results were that initiation of the iLA resulted in prompt and marked reversal of hypercapnia, allowing less aggressive ventilation. The mortality rate (37/90) was less than predicted based on the Sequential Organ Failure Assessment score. The Novalung iLA 2011 registry report, available on the Novalung website, presents data from 2007-2011 for 600 patients treated with the Novalung iLA. The data in this report shows statistically significant clinical benefit of therapy in PaCO2 reduction, pH correction, and ultra-protective ventilatory settings. The Novalung Compendium of Evidence, also available on their website, references several further literature reports which provide support for the use of ECCO2R therapy for ARDS, acute exacerbation of COPD, bridge-to-lung transplant, weaning from mechanical ventilation, and H1N1.

There are also limited reports of another low-flow ECCO2R device, the Hemodec DECAPsmart, which has equivalent indications for use to the Hemolung and Novalung iLA. In 2006, Livigni et al reported on the use of a low-flow veno-venous carbon dioxide removal device (the Hemodec DECAPsmart) in 7 adult sheep. The animals were anesthetized, intubated and ventilated with a protective minute volume which resulted in hypercapnia (PaCO2 > 70 mmHg), then connected to the device using a veno-venous circuit. ECCO2R produced an average reduction in PaCO2 of 17%-22% with no observed adverse events. The first report of the use of this device in humans was published by Terragni et al in 2009. This report assesses 32 patients (>18 years) with a diagnosis of ARDS who were treated for 72 hours with the ARDSNet strategy for lung protective ventilation, then evaluated for efficacy of the ARDSNet protocol. Patients failing this strategy were placed on ECCO2R using veno-venous access with a 14F dual lumen catheter. Blood flow was pump driven at 500 ml/min and anticoagulation was systemically administered to maintain an aPTT of approximately 1.5 times baseline. Ten of 32 subjects met the criteria for therapy with ECCO2R. The results showed for all ten patients that ECCO2R allowed for normalization of PaCO2 and pH, and that it allowed for further reductions in tidal volume below ARDSNet protocol, which were associated with reductions in plateau pressures and pulmonary inflammatory markers compared to the patients treated only with mechanical ventilation using the ARDSNet protocol for lung protective ventilation.

In addition to reports of other modern ECCO2R systems, Batchinsky et al reported on the use of the Hemolung RAS in a third party study to investigate the ability of the Hemolung to reduce minute ventilation while maintaining normocarbia in seven sedated swine. In this report, titled “Respiratory dialysis: Reduction in dependence on mechanical ventilation by veno-venous extracorporeal CO2 removal”, veno-venous CO2 removal by the Hemolung enabled a 50% reduction in minute ventilation while maintaining normocarbia. Further publications of the Hemolung human clinical feasibility study are currently under review.

Several recent review articles have been published supporting the safety and feasibility of ECCO2R therapy for the partial support of acute reversible respiratory failure. These include:

3. “Carbon dioxide dialysis will save the lung” by Pesenti, Patroniti and Fumagalli (2010).
4. “We do not need mechanical ventilation any more” by Del Sorbo and Ranieri (2010).


   In their review of “Extracorporeal CO₂ Removal”, Terragni et al conclude, “With improved technology and experience, low extracorporeal blood flow with high performance ECCO₂R may be the key to management of severe ARDS with a new respiratory support, shifting from invasive mechanical ventilation to the application of extracorporeal lung support, similar to renal support”.

Bibliography


Why can extracorporeal membrane gas exchange devices provide clinically effective carbon dioxide removal at low flow rates, but not clinically useful oxygenation?

There are primarily three reasons for this observation:

1. Carbon dioxide (CO₂) is 20 times more soluble in blood than oxygen (O₂). This means that there is much less resistance to CO₂ dissolving in and out of blood which makes it more readily exchangeable.

2. The slope of the CO₂ dissociation curve for blood is much steeper than that of the O₂ dissociation curve in the range of blood gas pressures where gas exchange typically occurs. This means that for a unit change in partial pressure, much more CO₂ is exchanged compared to O₂. This will be explained in more detail below.

3. In an extracorporeal device, the difference in the partial pressure of CO₂ between the blood and the gas phase, which is the driving force for gas exchange, can be appreciably increased compared to what occurs naturally in the lungs, and because of the steep slope of the dissociation curve for CO₂, this can substantially increase the amount of CO₂ removed. For O₂, the difference in partial pressure of O₂ between the gas phase of the artificial lung and the blood can also be increased but despite higher O₂ partial pressures, the hemoglobin is already saturated with O₂ so the increased pressure gradient has little overall effect on the total amount of O₂ added to the blood.

The average basal rate of oxygen consumption by the human body is approximately 250 mL/min, whereas the average basal rate of production of CO₂ is approximately 200 mL/min. These rates can of course vary largely and rapidly in response to many factors such as exercise, stress, or illness.

Oxygen and CO₂ are carried in the blood both in the dissolved form and in equilibrium with other chemical combinations. For CO₂, only 7% of the total content in blood is in the dissolved form, while 70% is carried in the form of bicarbonate (HCO₃⁻), and 23% in a combined form with hemoglobin (carbaminohemoglobin). As the partial pressure of CO₂ dissolved in blood increases or decreases while travelling through the lungs or capillaries, the reaction of CO₂ to bicarbonate and carbaminohemoglobin is driven in the corresponding direction thus unloading or absorbing large reserves. Likewise for O₂, only 3% of the total content is carried in the dissolved form, and 97% is carried by the hemoglobin molecules in the red blood cells. Figures 1 and 2 show the dissociation curves for both CO₂ and O₂, which represent the total content of each gas in blood as a function of the partial pressure of each gas dissolved in blood. As the partial pressure is reduced, gas molecules disassociate from the different forms they are carried in.

Unlike CO₂, the carrying capacity of blood for O₂ is limited by the total hemoglobin concentration and by the limited amount of O₂ that each hemoglobin molecule can carry. This is reflected by the plateau of the O₂ dissociation curve (see Figure 1 below). Above a pO₂ of 100 mmHg, all of the hemoglobin molecules are saturated with O₂, and any additional oxygen can only be carried in the dissolved form which is a negligible fraction of the total content. In contrast, CO₂ only needs water to form HCO₃⁻ which is not a limiting factor. The reaction of CO₂ to HCO₃⁻ is facilitated by the presence of carbonic acid in the
red blood cells; it does not combine with CO₂, it facilitates the reaction, thus it is only a limiting factor in the case of low hematocrit.

The basal rate of production of CO₂ corresponds to an additional 4 ml of CO₂ carried in each 100 ml of blood (or 4 volume percent) back to the lungs to be ventilated. When venous blood enters the lungs, its partial pressure is approximately 45 mmHg, under normal conditions, which corresponds to a total CO₂ content of 52 volume percent (see the CO₂ dissociation curve in Figure 2 below).¹ The partial pressure of CO₂ in the alveoli under normal lung respiration conditions is 40 mmHg. Because of the large surface area for gas exchange in the lungs and the small capillary diameter, CO₂ exchange within the lungs is able to reach equilibrium, meaning that the partial pressure of CO₂ in the blood as it exits the lungs has the same concentration as in the alveoli, or 40 mmHg. Referring to the dissociation curve, this corresponds to a total CO₂ content of 48 volume percent. Thus the lungs are able to unload 4 volume percent, or 4 mL per 100 mL blood. Multiplying this quantity by the average cardiac output of 5 L/min equals 200 ml of CO₂ per minute removed by the lungs, the same as the CO₂ production rate by the body. If the body produces more CO₂, the higher concentration of CO₂ in the blood not only increases the pressure gradient across the lung capillaries driving a greater rate of diffusion, but it also triggers an increase in the rate of breathing which reduces the partial pressure of CO₂ in the alveoli, thus maintaining homeostasis.

In the Hemolung, blood entering the device is typically hypercapnic with a partial pressure of 50 – 100 mmHg. The partial pressure of CO₂ in the sweep gas flowing through the fiber lumens is zero, if the flow is maintained sufficiently high (> 9 L/min). This creates a substantial increase in the CO₂ pressure gradient driving diffusion of CO₂ out of the blood and in to the fiber lumens. In contrast to the lungs, the total surface area for gas exchange in the Hemolung cartridge is much less (0.59 m² versus 160 m²), and the thickness of the blood boundary layer adjacent to the fiber surface compared to the small capillary diameter in the lungs (8 microns), is much greater. This results in the Hemolung CO₂ exchange being dependent on the flow patterns of the blood adjacent to the membranes and the residence time of the blood in the gas exchange portion of the cartridge. Unlike in the lungs, the partial pressure of CO₂ in the

blood is not able to reach equilibrium with the partial pressure in the sweep gas. Despite this limitation, the large difference in partial pressure drives the removal of significant amounts of CO₂. For the Hemolung at a blood flow of approximately 500 mL/min, the partial pressure of CO₂ exiting the cartridge is between 20 – 40 mmHg, depending on the inlet pressures. For an inlet CO₂ pressure of 70 mmHg, the outlet pressure would be approximately 30 mmHg. Referring to the CO₂ dissociation in Figure 1, this would correspond to a reduction in the blood’s CO₂ content from 60 volumes per cent to 40 volumes percent, or a 20 volume percent net reduction. Multiplying 20 ml CO₂ per 100 mL blood times the flow rate of 500 mL/min shows a removal of 100 ml CO₂ per minute, or approximately 50% of the basal CO₂ production rate.

In contrast to CO₂, the amount of O₂ that is removed by the Hemolung is not as great. The inlet partial pressure of oxygen to the Hemolung would be approximately 40 mmHg which corresponds to an oxygen content of 15 volume percent. Because the sweep gas through the fibers is 100% oxygen, the partial pressure would be approximately 700 mmHg in the sweep gas, which provides a substantially greater partial pressure gradient driving diffusion of oxygen into the blood. The Hemolung is able to fully oxygenate the blood flowing through the device because of this large driving gradient, and the partial pressure of O₂ in the blood exiting the cartridge reaches approximately 250 mmHg. However, even if the partial pressure was able to fully equilibrate to 700 mmHg, the total content in the blood can only increase to 20 volume percent, because the hemoglobin molecules become saturated with oxygen at 100 mmHg pO₂. The quantity of blood carried in the dissolved form, even at partial pressures of 600 mmHg, would be a very small fraction of the total content carried by the hemoglobin. Therefore the change in oxygen content provided by the Hemolung would be 5 ml O₂ per 100 ml blood, which after multiplying by the blood flow rate of 500 mL/min, corresponds to an oxygenation rate of 25 ml O₂ per minute. Even though some oxygenation is occurring, it only represents approximately 10% of the total basal oxygen demand.

For the above detailed reasons, ECMO systems used to provide significant portions of the overall basal oxygen demand requires much higher flows and larger surface area gas exchangers compared to ECCO₂R systems. In turn, these conditions necessitate the use of additional circuit components including a heat exchanger, a more powerful pump and other relevant safety equipment. This level of complexity and risk is unnecessary for the partial removal of basal CO₂ production.