Review Article

Extracorporeal life support for acute respiratory distress syndrome

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Abstract:

The morbidity and mortality of acute respiratory distress syndrome remain to be high. Over the last 50 years, the clinical management of these patients has undergone vast changes. Significant improvement in the care of these patients involves the development of mechanical ventilation strategies, but the benefits of these strategies remain controversial. With a growing trend of extracorporeal support for critically ill patients, we provide a historical review of extracorporeal membrane oxygenation (ECMO) including its failures and successes as well as discussing extracorporeal devices now available or nearly accessible while examining current clinical indications and trends of ECMO in respiratory failure.

Key words:

Acute respiratory distress syndrome, extracorporeal life support, extracorporeal membrane oxygenation

The initial mortality rates associated with acute respiratory distress syndrome (ARDS) were reported to be as high as 50% in 1967.[1] Published studies in the early 1990s demonstrated a reduction in mortality that continued to a nadir of 29-38% by the end of the decade.[2-6] More recently, the mortality associated with ARDS has remained steady at 25-30%.[7,8] In a recent study, there was no difference in mortality rates between early- and late-onset ARDS.[9] Although this reduction in ARDS mortality is not universally accepted, there has been some progress in the treatment of acute lung injury (ALI) and ARDS. This progress is directly related to the methods of respiratory support employed in the treatment of critically ill patients with ARDS. In this manuscript, we review the changes in conventional mechanical ventilation before moving onto methods of extracorporeal support. We discuss early failures and more recent success of extracorporeal membrane oxygenation (ECMO), while discussing alternative extracorporeal devices currently available or soon to be accessible. To conclude, we briefly discuss the current clinical applications and recent trends for the use of ECMO.

Conventional Respiratory Support for Acute Respiratory Distress Syndrome

Typically, therapeutic strategies hinge on the knowledge of the underlying disease process, but our understanding of ARDS is very limited. Despite our limited understanding of the pathophysiology, numerous clinical trials, including the ARDS network trial, suggested that specific ventilator management techniques could lead to superior outcomes.[10] Lung protective ventilation with adjusted positive end-expiratory pressure (PEEP) remains the most effective respiratory support method. It is now clear that high tidal volumes result in further lung injury and that the use of lower tidal volumes (6 ml/kg) may improve mortality.[10-14] Mechanical ventilation with lower tidal volumes, resulting in higher than normal CO_2 partial pressures (permissive hypercapnia), is associated with not only a reduction in mortality but also a less number of days requiring ventilator use. The complications and mortality of severe lung injury and ARDS remain very high at 35-45%.[15]

A major reason for the slow progress in advancement of the treatment of ALI and ARDS is the lack of detailed knowledge of the pathophysiology of ARDS and the impact upon this physiology by the current treatment strategies. The current trend of permissive hypercapnia is constrained by the limits of tolerable respiratory acidosis which may cause substantial changes in hemodynamic function and organ blood flow unless the arterial pH is controlled.[16,17]

In refractory ARDS with profound hypoxemia or respiratory acidosis, additional non-pharmacological interventions are necessitated, such as positioning maneuvers, nitric oxide, reverse inspiratory:expiratory ratio ventilation strategies, airway pressure ventilation, partial liquid ventilation, or high-frequency ventilation techniques. Additionally, the use of extracorporeal support is now starting to be used more commonly. Extracorporeal technology may benefit this patient population by facilitating

gas exchange without the harm associated with aggressive mechanical ventilation. Extracorporeal life support is a modified form of cardiopulmonary bypass used to provide prolonged gas exchange in patients with respiratory and/or cardiac failure. The devices require fairly large cannulas for continuous pumping of blood from the patient to a membrane oxygenator. In addition to oxygenation, CO_2 can be efficiently removed with extracorporeal technology. A major limitation of this complicated form of intensive care is the need for anticoagulation to prevent blood clotting.

Extracorporeal membrane oxygenation in ARDS

In 1972, Hill *et al*. published the first case report that used ECMO in a patient who suffered from ARDS due to acute post-traumatic respiratory failure. At that time, mortality rates from ARDS were exceedingly high, and the idea of extracorporeal support in this population showed great promise.[18] However, a randomized controlled trial using ECMO in ARDS demonstrated mortality rates of >90% in both treatment arms.[19] Although this was a landmark paper by Zapol *et al*.[19] at that time, it suffered from significant flaws, including the use of only veno-arterial (VA) ECMO, termination of ECMO after 5 days was an option if no improvement occurred, significant problems with bleeding, the lack of "rest" ventilator settings, and the lack of experience of many participating centers. Despite these dismal results, several investigators continued to work in the area of extracorporeal devices and strategies. Extracorporeal CO_2 removal paired with a novel ventilation strategy at that time, low-frequency positive pressure mechanical ventilation, demonstrated some improvement in results.[20-23] However, a randomized controlled trial failed to demonstrate an actual survival benefit from extracorporeal CO_2 removal in ARDS, although the survival rates were substantially improved as compared to the 1970s.[24] Survival rates were 33% for the extracorporeal group and 42% for the conventional mechanical ventilation group.[24] The investigators were unable to show a survival benefit as the cohort study was small (n = 40) compared to the ARDS network trial on low tidal volumes that stopped recruitment after enrolling 861 patients.

Early poor outcomes with extracorporeal membrane oxygenation in ARDS

The lack of any substantial impact upon mortality in these early studies with extracorporeal CO_2 removal in ARDS is multifactorial. Early extracorporeal CO_2 devices were limited in their technology. In addition, ventilation strategies differed substantially at that time compared to today where low tidal volumes and airway pressure gradients are now used for protective ventilation.[10,11,25,26]

Extracorporeal devices continue to be used more frequently than ever before in intensive care units throughout the world. With advancements in technology, the new devices are less prone to complications. In addition to technological progress, there has been improvement related to the clinical application of extracorporeal support devices in individual patients, including early introduction and strategies for changing from devices as clinically indicated.[27,28]

Recent outcomes with ECMO in ARDS

The recent report of successful ECMO support in older patients inflicted with H1N1 influenza increased interests in the use of this mode of support in adult patients with severe respiratory failure.[29] Also that same year, the conventional ventilatory support versus ECMO for severe adult respiratory failure (CESAR) study was published. The investigators used a "pragmatic" study design and were criticized for the inability to standardize mechanical ventilation management in the conventional care group.[30] Importantly, the CESAR trial demonstrated that protocolized care that included ECMO in an expert center for ARDS care yielded higher survival than the best standard care in tertiary intensive care units in the UK.[30]

Innovations in ECMO

In the 1960s, a milestone in the technological evolution of ECMO was the development of membrane oxygenators, which began replacing bubble oxygenators. Membrane oxygenators provided gas exchange with the benefits of increased short- and long-term biocompatibility. The recently developed membrane-type oxygenators were less harmful as blood was exposed to oxygen through a gas-permeable membrane, which enhanced gas transfer compared to the bubble oxygenators. At the end of the 1990s, a silicone covering of the microporous polypropylene hollow fibers was used that had a heat exchanger and oxygenating compartment with a polymethylpentene (PMP) membrane in a small polycarbonate shell.[31] Development of the PMP oxygenator has proven to be an important advancement in ECMO technology as the PMP oxygenators have slowly replaced both the silicone membrane and polypropylene microporous oxygenators.[32,33] The PMP oxygenators result in a reduction of the need for red blood cell and platelet transfusions, provide better gas exchange, have lower resistance and priming volumes compared to silicone membrane oxygenators, and have less oxygenator failure compared to polypropylene microporous oxygenators.[34] The development of heparin-coated circuits allows for extracorporeal support with decreased platelet, complement, and granulocyte activation with reduced heparin requirements.[35,36] New generation centrifugal pumps permit support with essentially no risk of tubing rupture with a smaller priming volume and potentially reduced need for a reservoir.[37] Yet, another major innovation that has truly enhanced the capability of extracorporeal CO_2 removal was the development of a bicaval dual-lumen catheter (Avalon Laboratories, Rancho Dominguez, CA, USA) that allows respiratory support through a single catheter for application of ECMO.[38]

Different modes of ECMO

In the setting of complete cardiopulmonary support, conventional VA ECMO is primarily used while primary respiratory failure, including severe oxygenation failure, is treated with veno-venous (VV) ECMO. Hypercapnic respiratory failure can be treated with either a VV or a VA approach. Both VV and VA approaches require a pump that is capable of generating flow rates of 3-5 l/min to assure sufficient organ perfusion and oxygenation in the adult size patient. Figure 1 illustrates the different cannulation strategies for the variable forms of ECMO support (VA, VV, and double lumen VV) currently used in patients. An arterio-venous (AV) approach can be used as well which does not require a pump. In specific circumstances, low-resistance devices can be used which allow sufficient blood flow driven by the systemic blood pressure from the patient. These pumpless extracorporeal lung assist (PECLA) devices achieve flow rates of 0.8-1.5 l/min allowing for sufficient CO_2 removal.

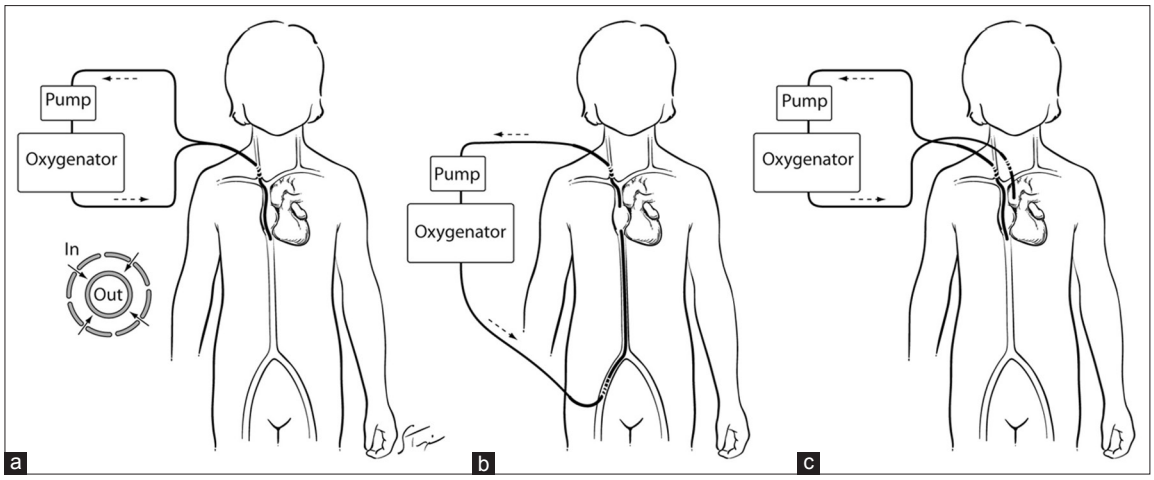

Figure 1: Three configurations of extracorporeal blood flow (a) single-site double lumen veno-venous (VV), (b) two-site VV, and (c) veno-arterial

Alternative extracorporeal devices

Arterio-venous CO_2 removal

An AV shunt for extracorporeal gas exchange can potentially reduce the complexity of conventional ECMO, while allowing for gas exchange to achieve near total removal of CO_2. The technique of extracorporeal AV CO_2 removal ($AVCO_2R$) was developed using a low-resistance, commercially available, hollow fiber gas exchanger to provide lung rest in the setting of severe respiratory failure.[39] Although $AVCO_2R$ is efficient in CO_2 removal, it does not provide any substantial oxygen transfer. The initial human study with $AVCO_2R$ included five adult patients with ARDS and CO_2 retention with percutaneous $AVCO_2R$ achieving approximately 70% CO_2 removal in the cohort without hemodynamic compromise or instability, while oxygenation was successfully managed with gentle ventilation and near-apneic oxygenation.[40] All of these patients survived the study period without adverse sequelae and only minor complications.[40]

PECLA, Novalung®, and interventional lung assist (used interchangeably)

The early success of $AVCO_2R$ intensified the interest and increased the use of $AVCO_2R$ in Europe, which is termed PECLA, interventional lung assist (ILA) device, or Novalung® (Novalung GmbH, Talheim, Germany). These devices have a circuit that uses a hollow fiber gas exchanger without the need for a pump.

An *in vivo* study with an ovine model was undertaken to determine the efficacy of the Novalung® circuits in the short-term removal of CO_2 and to assess hemodynamic responses.[41] The animal was cannulated in the jugular vein and carotid artery for 72 h.[41] The Novalung® device provided near total CO_2 removal (mean: 119.3 ml/min) with device blood flow rates (Qb), 1 l/min; sweep gas flow rates (Qg), 5 l/min; and P_aCO_2, 40-50 mmHg.[41] The P_aCO_2 level was also found to be directly proportional to the CO_2 clearance for the device.[41] In another *in vivo* study with a pig model, ILA was studied to determine the device's ability to improve oxygenation with cannulation through both femoral arteries and one femoral vein with the animals anesthetized and mechanically ventilated.[42] With the application of ILA, the arterial partial pressure of oxygen was increased from 64 ± 13 mmHg to 71 ± 14 mmHg and 74 ± 17 mmHg with blood flow through one and two femoral arteries, respectively.[42] The increase in oxygenation was small, but was significant; thus, the results indicated that ILA may not be warranted if oxygenation is the primary therapeutic goal.[42] Two further studies demonstrated that the Novalung® device provided adequate gas exchange without hemodynamic instability with static ventilation at PEEP pressures ≥10 cm H_2O.[43,44] A third animal study, using an ARDS model, was performed to prospectively evaluate the effects of ILA on hemodynamics and gas exchange in cardiopulmonary resuscitation.[45] Ventricular fibrillation was induced in the lung injured, mechanically ventilated pig with chest compressions starting immediately and continuing for 30 min in the anesthetized animals.[45] The experimental group (open ILA system) showed a marked decrease in P_aCO_2 and increase in P_aO_2 without a significant difference in systolic and mean blood pressure compared to the control group (clamped ILA system).[45]

The Novalung® system has been investigated in Europe since 1996 and has been established as a therapeutic measure for a variety of lung conditions. In one study, the Novalung® was used easily and inexpensively used in 1,800 patients for artificial lung assistance.[46] Furthermore, the PECLA device was effective at oxygenation and CO_2 removal in 70 patients with severe respiratory failure of various etiologies.[47] A 10-year-review outlined experience in 159 patients ranging in age from 7 to 78 years who were treated with PECLA for ARDS (70.4%) and pneumonia (28.3%).[48] The study had a cumulative experience of over 1,300 days.[48] During the study period, the overall mortality was 48.7%, mostly attributed to multiorgan failure.[48] Inability to stabilize pulmonary function was noted in only 3% of patients, and the 30-day mortality after PECLA was 13.6%.[48] Numerous case reports, retrospective analyses, and prospective studies have validated the PECLA for use as a therapeutic measure for CO_2 removal in a wide variety of etiologies of acute respiratory failure including ARDS[49-67] and as a bridge to lung transplantation.[52-56] The PECLA system has been proven to be superior to lung assist devices that require a pump because it significantly reduces bleeding, hemolysis, and mechanical trauma to the blood.

A multitude of studies have demonstrated that the Novalung® facilitates the reversal of hypercapnia, while stabilizing oxygenation with the only reported complication being reversible distal limb ischemia.[68-80] In a large cohort study with 96 patients with severe ARDS, the application of ILA significantly increased the P_aO_2/FiO_2 ratio, while improving the P_aCO_2 and pH within 2 h in all patients.[81] The ILA eliminated approximately 50% of calculated total CO_2 produced with rapid normalization of respiratory acidosis.[81]

Despite extensive study, the main disadvantages of ILA are arterial damage, immobilization, and cardiovascular steal. Therefore, newer technology was needed and has continued to evolve with the most device released being ILA activve® (Novalung GmbH, Talheim, Germany).

Intravenacaval (intravascular) oxygenator and CO_2 removal device

Mortensen developed the concept of an intravenacaval (intravascular) oxygenator and CO_2 removal device (IVOX) as an intracorporeal gas exchange device in patients with ARDS.[82,83] The components of IVOX include multiple hollow fibers, that are silicone coated and heparin bonded, to create a thin membrane, which are then placed in the vena cava to provide blood oxygenation and CO_2 removal, without the need for extracorporeal circulation or blood transfusion. The fibers join together in a manifold that communicates with the dual-lumen gas conduit at both the proximal and distal ends.

In animal models, implantation of the IVOX device did not adversely affect hemodynamic function and there was no evidence of significant hemolysis, thromboembolism, foaming in the blood, catheter migration, or vena caval intimal injury.[84-87] In the initial design, the IVOX was capable of removing up to 30% of CO_2 production in an ovine model (normal: 150-180 ml/min) of severe smoke inhalation injury.[84] The IVOX device was easy to use, but generated somewhat variable results, for instance when there were changes in cardiac output, instability in metabolism, or compensation in respiration. The IVOX device has had limited capacity in comparison to natural lungs.[87] The IVOX device in animal and human studies has demonstrated an average of 40 ml/min of CO_2 removal and oxygen exchange, approximately 25-30% of the metabolic demands of the patients implanted with the device.[85,86] The end result was that IVOX could not be recommended as an alternative for ECMO or provide total support for patients with acute respiratory failure.

An international multicenter Phase I-II clinical trial of IVOX with a total of 164 IVOX devices used in 160 patients with acute respiratory failure, due to a variety of causes (lung infection, trauma, sepsis, and ARDS), found an immediate improvement in blood gas findings in a majority of patients, which allowed for a reduction in ventilator settings.[88] The overall survival of patients who were treated with the IVOX device was only 30% and was directly related to the severity of lung injury and patient selection. Device complications included mechanical and/or performance problems and user errors, whereas patient complications included bleeding, thrombosis, infection, venous occlusion, and arrhythmias.[88] Due to these experiences with IVOX, significant improvements are needed in the design and engineering of the device in order for it to become more clinically applicable.

Intravascular lung assist device

The intravascular lung assist device (ILAD) was designed by placing the membrane fibers into sub-units of rosette-like layers, with a surface area of 0.4-0.6 m^2 perpendicular to blood flow with the same intravascular placement.[89] The device achieved 100 ml/min of both oxygen and CO_2 exchange, but the blood pressure gradient required to overcome the resistance of the device to attain this gas exchange was high (23-105 mmHg). Further attempts were unsuccessful with the fibers in a helical form.[90] Unlike conventional devices which depend on passive bulk blood flow around them, this "pumping" ILAD causes an active driving force for the blood when rotated.

Hattler respiratory assist catheter

The Hattler respiratory assist catheter incorporates a small pulsating balloon into the middle of a hollow fiber bundle. Functioning characteristics of the device have been studied *in vivo* and *in vitro* studies.[91] The balloon allows for convective mixing of the blood and thus increases gas exchange. A larger balloon volume and higher pulsation rate have been shown to increase both oxygen loading and CO_2 removal in a linear fashion in an *in vitro* model.[91] In another study, application of a random balloon pulsation did not significantly impact gas exchange within the respiratory assist catheter.[92] Despite these advances, the clinical use of an intravenous respiratory assist device is impeded by the insertion diameter of the catheter due to the catheter being dependent upon the critical number of hollow fiber membranes necessary to achieve gas exchange. The current catheters being prepared for human clinical trials require an insertion size of 32 Fr, even with optimal gas exchange efficiency of the pulsating balloon. Therefore, efforts are moving forward with the development of an impeller percutaneous respiratory assist catheters (iPRAC) with an insertion size <25 Fr.[93] The limitation to the clinical application of this sort of a catheter is the ability to protect the vascular endothelium from rotating fibers.

The latest concept in respiratory assist catheters is the development of iPRAC. The new design incorporates rotating impellers within a stationary bundle of hollow fiber membranes. Active mixing by rotating impellers produced 70% higher gas exchange efficiency than pulsating balloon catheters.[94] The iPRAC catheter has a diameter of 25 Fr and surface area of 0.07 m^2 with no adverse effects on hemodynamic function in laboratory animals. Even though the CO_2 removal efficiency of the iPRAC is currently the highest of any respiratory assist catheter, improvements are still needed before it can be used as a clinical device. Future studies will need to address optimal blood flow and gas exchange through the catheter and long-term efficacy of CO_2 removal while assessing novel hollow fiber membrane coatings to facilitate additional CO_2 removal.[94]

Decap and hemolung respiratory assist system®

More recently, the modification of a continuous VV hemodialysis machine was introduced that solely performs decapneization (CO_2 removal) in conjunction with hemofiltration in a system called DECAP/DECAPsmart (Medica S.p.A., Medolla, Italy).[95] For intravascular access, a single double lumen cannula is inserted into the femoral vein with blood flow achieved by a non-occlusive roller pump with blood circulating through a membrane oxygenator then a hemofilter. Although this system does not allow for total gas exchange, it may augment

CO_2 removal that would further permit reduction of minute ventilation. Extracorporeal CO_2 removal devices have been used in a Phase II study supporting the use of this technology in patients with severe ARDS who fail a trial of protective ventilation.[96] Similar dialysis-like systems are infiltrating the market now, including the Hemolung Respiratory Assist System® (ALung Technologies, Inc., Pittsburgh, PA, USA).

Clinical indications of ECMO

Figure 2 illustrates three key components of an ECMO circuit: The oxygenator, better bladder (venous compliance chamber) if used, and bubble detector. The oxygenator facilitates gas exchange and the better bladder controls pump flow as a function of inlet pressure, while bubble detection is a vital preventative measure. Guidelines describing indications and the practice of ECMO are published by the Extracorporeal Life Support Organization.[97] The generally accepted criterion for the initiation of ECMO is either acute severe cardiac or pulmonary failure or combination of both that is potentially reversible and unresponsive to conventional management. Examples of these clinical situations include the following etiologies: Hypoxic respiratory failure with a ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) <100 mmHg despite optimal settings on mechanical ventilation, hypercapnic respiratory failure with an arterial pH < 7.20, refractory cardiogenic shock, cardiac arrest, failure to wean from cardiopulmonary bypass after cardiac surgery, and as a bridge to either heart or lung transplantation. Depending on the clinical situation, ECMO can even be implemented at the bedside of a patient [Figure 3].

Clinically, VA ECMO provides complete cardiorespiratory support by extracting blood from the right atrium and returning it to the arterial system, therefore bypassing the heart and lungs. Contrasted to a VV approach, blood is extracted with VV ECMO from the vena cava or right atrium and returned to the right atrium with the patient still dependent on their intrinsic biventricular cardiac performance for hemodynamic support. Characteristically, VA ECMO is used for cardiac or combined cardiopulmonary failure, and VV ECMO is used for respiratory failure. The results of VV ECMO support for respiratory failure are similar to outcomes compared to VA ECMO, but with less morbidity secondary to improved neurological outcomes and preservation of arterial blood vessels.[98-102]

As discussed earlier, the development of a bicaval dual-lumen catheter (Avalon Laboratories, Rancho Dominguez, CA, USA) allows for respiratory support via application of ECMO through a single catheter site.[38] The catheter is inserted from the right jugular vein into the superior vena cava, traversing the right atrium to the inferior vena cava where it drains venous blood from both the superior and inferior vena cava and then directs oxygenated blood into the right atrium toward the tricuspid valve. The single site application of this method of VV ECMO in the neck permits ambulation and oral nutrition and has been used in patients as a bridge awaiting lung transplantation.[103-106] The theory behind this methodology of ambulatory ECMO [Figure 4] in patients with advanced lung disease requiring lung transplantation is to optimize both physical rehabilitation and nutrition prior to lung transplantation. To our knowledge, the use of ambulatory ECMO has not been attempted in ARDS, but the use of a simple circuit with the capability of total or near-total gas exchange should be considered in this population and may be a potential therapeutic option to liberate ARDS patients from mechanical ventilation.

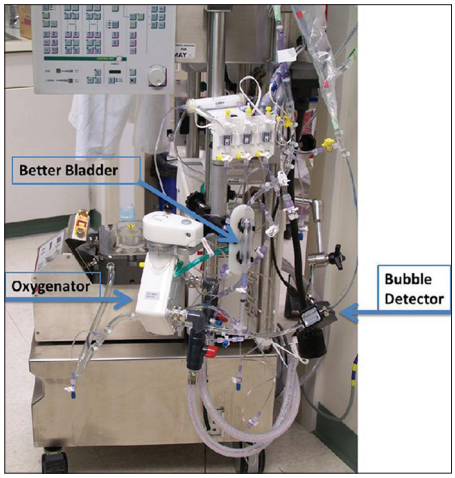

Figure 2: An extracorporeal membrane oxygenation circuit with the oxygenator, better bladder, and bubble detector

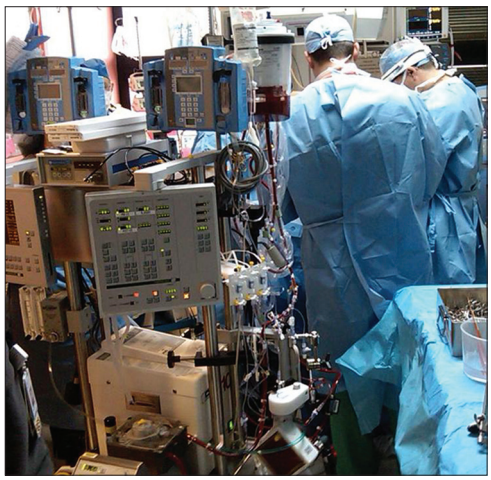

Figure 3: Implementation of veno-arterial extracorporeal membrane oxygenation at the beside of a patient

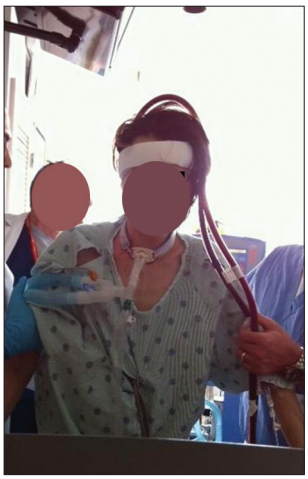

Figure 4: Ambulatory extracorporeal membrane oxygenation with single-site double lumen veno-venous approach being used in a patient as a bridge for lung transplantation

Conclusions

Extracorporeal treatment modalities are showing promise in the management of ARDS and are being increasingly used in intensive care units as rescue therapies in patients with ARDS who fail to respond to conventional mechanical ventilation. Patient selection and timing of the application of the extracorporeal device continue to be very important determining factors in the eventual outcome. The technology of the current devices is slowly evolving into smaller systems and will likely continue to shrink in size. As the risk of these devices decreases, their role in ARDS may increase but continues to not be well defined presently with further research needed in this patient population.

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