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SURGICAL SYMPOSIUM CONTRIBUTION

ECLS in Trauma: Practical Application and a Review of Current Status

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Abstract Extracorporeal life support has evolved considerably over the past two decades. Once considered as salvage or experimental therapy in adults, extracorporeal membrane oxygenation (ECMO) is evolving into a mainstream treatment for adult critical care. This is especially true in trauma and high-risk surgical patients, who have traditionally been excluded from consideration. Several technological advances have made this possible. This includes anticoagulant-bonded circuits, device miniaturization, servo-regulated centrifugal systems, and more efficient oxygenators. Adult ECMO may now be rapidly deployed for severe acute respiratory distress syndrome (ARDS) and cardiogenic shock. Trauma and surgical patients with severe ARDS should be considered for ECMO early in their clinical course to provide optimal lung rest.

Introduction

Extracorporeal life support (ECLS) for adults, and extracorporeal membrane oxygenation (EMCO) in particular, has evolved considerably over the past two decades. Once considered as salvage or experimental therapy in adults, ECMO is evolving into a mainstream treatment for adult critical care. As of December 2015, close to 20,000 adults have been treated with ECMO. No doubt, ECMO remains a high-risk, low-volume, critical care endeavor in most intensive care units. In the context of improving mortality, patients, families, and physicians should still be aware of the realistic odds of both survival and good functional outcome (Table 1).

The question of where ECMO fits into the respiratory failure treatment strategy for high-risk patients continues to be heavily debated, with proponents and detractors on both sides of the issue. In most surgical intensive care units, severe respiratory failure for acute respiratory distress syndrome (ARDS) is treated in a rather prescriptive way. Based on the best available evidence, most intensivists will initiate some version of a lung-protective strategy based on the ARDS net strategy [1]. Failing this, patients may receive neuromuscular blockade and prone positioning [2, 3]. Progressive hypoxic failure may necessitate alternate ventilation options to include high-frequency oscillatory or high-frequency percussive ventilation [4, 5]. Failing a ventilation strategy change, additional adjunctive measures such as a forced lung water diuresis, inhaled nitric oxide administration, prostacyclin inhibition, and surfactant administration may be employed. After days of attempting such typical strategies in persistently hypoxic patients, consideration may be finally given to extracorporeal respiratory support. Perhaps as one of the most lung-protective strategies, ECMO is often considered late in the patient's clinical course. This is especially the case when the bleeding risk is high or the complex surgical nature of disease traditionally precludes consideration. However, in the past several decades, significant improvements have been made with both the technology and patient safety profile. Especially in high-risk trauma patients, consideration should be given to an earlier institution of such a

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Table 1 ELSO adult registry international summary (1990–2015)

	Patients	Survive ECLS (%)	Survive to discharge (%)
Respiratory	9102	5989 (66)	5254 (58)
Cardiac	7850	4394 (56)	3233 (41)
E-CPR	2379	948 (40)	707 (30)

E-CPR (ECMO-supported Cardiopulmonary resuscitation)

treatment. Because of improving results, many would argue that early implementation of ECMO for severe respiratory failure with the premise of maximal lung protection should be seriously considered.

Early beginnings

It is relevant to review the history of adult ECMO and place indications and outcomes in both the historic and modern context of respiratory and cardiac support for high-risk patients. First pioneered for adults in the early 1970s, initial outcomes had varied results. One of the first successful reports using ECLS for respiratory failure in an adult was in the year 1972. A 24-year-old male trauma victim was involved in a high-speed motor vehicle crash in Southern California. Presenting in extremis to a local emergency department, he was rapidly diagnosed with a thoracic-aortic dissection, complex pelvic fracture, and bilateral lower extremity fractures [6]. He was immediately taken to the operating room where he underwent aortic repair and stabilization of his fractures; postoperatively he developed what by today's definition would be severe ARDS. By his sixth postoperative day, he was supported on 100 % FiO_2 and large tidal volumes by conventional ventilation. When his PaO_2 declined to 38 mm Hg, his airway pressure climbed to >50 cm H_2O, oxygen saturation remained low, and it was determined that he would likely not survive. Determined to exhaust all resources, with the assistance of the U.S. Navy and surgeons from San Francisco, a somewhat experimental Bramson membrane lung was flown to the patient's bedside and he was placed on ECMO. After 75 h, the patient made sufficient recovery to be decannulated and ultimately survived. One must ask, though, did he survive because of the Bramson lung or despite the intervention?

Based on this index case and more than one-hundred reported cases (10–15 % survival), a randomized controlled trial was launched between 1974 and 1978 with nine participating clinical sites [6]. The trial examined the use of conventional-mechanical ventilation versus mechanical ventilation and ECMO support. After randomizing 90 patients, it was found that survival outcomes were poor in both groups (9.5 ECMO vs. 8.3 % conventional). Most of the patients enrolled in the study were diagnosed with severe pneumonia. In retrospect, one criticism was that many patients were enrolled after a week of intensive therapy, a problem we still observe today. Interestingly, there was a signal for possible survival advantage among those who were initiated early in their hospital course. Average blood loss was significant at 1–2 L a day. The technology in this negative trial was categorized with emerging critical care devices such as the hemodialyzer and the intra-aortic balloon pump. At that time, none of these devices demonstrated great outcomes but seemed promising. For nearly a decade, ECMO remained an unproven therapy.

In the mid-1980s, French researchers described extracorporeal carbon dioxide removal in concert with "lung rest." The concept of low-frequency positive-pressure ventilation and limited peak inspiratory pressure meant that CO_2 would inevitably concentrate [7, 8]. To control for developing hypercapnia, extracorporeal veno-venous support was provided to remove CO_2 in 43 patients (including trauma). Although 73 % of the patients had improved lung function over an average five-day run, the overall survival was a dismal 48 % [8]. In fact, trauma patients had the worst outcomes and similar to the previous trial, adult ECMO was deemed to be a futile therapy. A decade later, Morris randomized patients to either pressure-control inverse ratio ventilation with extracorporeal CO_2 removal or standard care [9]. This trial was halted after 40 patients when the overall survival rate was 30 %. Similar to previous trials, the major complications included significant hemorrhage with more than half of the group requiring greater than 800 mL of red blood cells per day. Hemolysis and transfusion requirements were due to high anti-coagulation needs.

The modern era of ECMO

Poor outcomes in each previously described trial were multifactorial. Notably, the technology was primitive by today's standards and anti-coagulation was fraught with unacceptable morbidity. However, in the late 2000s,

Table 2 Physiologic characteristics of veno-arterial & veno-venous ECMO

Characteristic	Veno-arterial	Veno-venous
Flow	Non-pulsatile	Pulsatile
Cardiac support	Yes	No
Systemic preload	Unchanged	Unchanged
Cardiac after load	Increased	Unchanged
Consequence of air micro-embolization	Systemic embolization	Lung micro-embolization
Target saturations	>80–90 % desired	>80 % desired
Recirculation risk	No[a]	Yes

[a] But do risk Harlequin syndrome

significant device changes were developed to augment complex critical care. Advances included device miniaturization, software improvements, and servo regulation. There was a transition from traditional roller pump technology, a legacy of cardiopulmonary bypass, to magnetic centrifugal impeller systems. Further, refinements in oxygenator efficiency and the ability to bond heparin to circuit tubing significantly reduced device malfunction. Access techniques also changed with a transition to percutaneous access versus traditional open vascular access.

The other important advancement was a growing clinical experience that arose from the H1N1 epidemic experience and the release of several cohort and clinical trials. During the 2009 H1N1 flu season, several ICUs in Australia and New Zealand used ECMO as a salvage therapy for severe hypoxic pneumonia. Among the 15 intensive care units reported in JAMA, 68 of the 201 mechanically ventilated patients were treated with extracorporeal support (63 veno-venous and 5 veno-arterial) [10]. With a mean support duration of 10 days, 53 patients (78 %) were able to be weaned from ECMO with an overall mortality of 21 %. Similar to other trials, more than half of the patients developed a bleeding complication during their ECMO run. During the same period in the UK, 80 patients with H1N1 were referred to four centers with ECMO capability [11]. Sixty-nine patients received support, with ten patients dying on support and ten dying after being liberated from support. A propensity analysis matching ECMO to non-ECMO patients who would have been referred was retrospectively performed. Investigators showed a 55 % relative risk reduction in the ECMO-supported group.

At about the same time, in the highly anticipated CESAR study, a UK-based randomized controlled trial, was published [12]. Despite being a controversial trial, 180 patients were randomized to the best available support versus referral to a specialized center for ECMO. As an intention to treat trial, 75 % of the patients referred to a single treatment center ultimately required support. The primary outcome was a six-month survival with measures of disability. Secondary outcomes included cost-effectiveness and cost-utility analyses. CESAR demonstrated a 21 % relative risk reduction for death or severe disability in the ECMO referral group. Further analysis demonstrated relative cost-effectiveness. Some of the well-described criticisms of this trial include the fact that this was a referral trial; that there was no standard treatment arm; there was no arm to examine ECMO transport; and the technology was not the most up-to-date as described above. Despite these limitations, not only was there a survival benefit, but also there was cost-effectiveness at 6 months with an improvement in the quality-adjusted life year. Many of these issues are being directly addressed in the EOLIA trial (ECMO for severe acute respiratory distress syndrome) which would be released in 2017 [13]. ECMO clinical trials remain difficult to undertake because most require multi-center participation and there remains significant heterogeneity in the approach to caring for these patients. The EOLIA trial, randomizing patients to early application of ECMO with established protocols in both treatment arms, will hopefully provide additional evidence of benefit.

ECMO in high-risk ICU patients

ECMO may now be rapidly deployed in two broad patient categories: those with severe ARDS refractory to conventional lung protection (veno-venous support) and patients with cardiogenic shock refractory to maximal medical therapy (veno-arterial support). Similarities and differences in therapeutic modality are summarized in Table 2. In most cases, cannulation may now be performed percutaneously and outside of the operating theater.

It is important to clearly define indications for extracorporeal support. In general, ECMO should only be considered for cardiac or pulmonary support in conditions that are either reversible or have a clearly defined pathway to a destination therapy. Because patients on ECMO can be sustained for days to weeks, a temporary bridge to decision-making may be a reasonable approach. But what remains unacceptable is a "bridge to nowhere." With the

overall goal of avoiding iatrogenic injury, ECMO may provide partial or total support. For cardiac support (veno-arterial ECMO), ECMO-qualifying cardiogenic shock is typically defined as inadequate tissue perfusion. This is manifest as hypotension despite adequate intravascular volume and refractory to inotropic support, vasoconstrictor support, and possibly other mechanical assist devices (e.g., intra-aortic balloon pump). Additional indications include cardiogenic shock after severe myocardial infarction, sepsis-associated cardiomyopathy, ECMO-supported cardiopulmonary resuscitation (E-CPR), and post cardiotomy cardiogenic shock [14–16]. A special consideration in VA support is an anticipated increase in cardiac after load. This must be addressed early in the patient's course and early consultation with cardiac surgery for possible venting of the left heart should be considered. Another special consideration is the risk of asymmetric blood flow resulting in a "harlequin syndrome." This observation of a cyanotic upper body and well-oxygenated lower body results from regional blood mixing-based native cardiac function, cannula position, and ECMO circuit flow. The greatest concern in this situation is cerebral hypoxia which should be assessed by measuring distal oxygenation (e.g., right radial artery). With high cardiac afterload and poor pulmonary function, this syndrome can be addressed by changes in the ECMO flow, cardiac venting, and alternate cannula positioning.

More typical in critically ill trauma and emergency surgical patients is veno-venous support for respiratory failure. Unlike VA support, native pulsatile flow is maintained without changes in cardiac afterload. Indications vary by center but typically include primary or secondary hypoxic respiratory failure refractory to traditional lung-protective strategies with an anticipated high mortality (e.g., >80 %). Table 3 demonstrates our center's inclusion criteria. Veno-venous implantation must be considered as a bridge to lung recovery from severe ARDS with a reversible provoking condition. If not reversible, a viable destination therapy (e.g., lung transplant) must be a feasible option. Objective calculator tools may assist the surgeon or intensivist to determine appropriate selection in addition to traditional markers of hypoxia (e.g., Murray score, oxygenation index). Just as important as inclusion criteria, optimal treatment should be provided with the consideration of defined absolute and relative exclusion criteria (Table 4).

Table 3 Inclusion criteria for veno-venous support

PaO_2: FiO_2 <120 with FiO_2 >90 % and PEEP >10
Oxygenation index (FiO_2 × MAP/PaO_2) >18
Severe hypercapnia not tolerable by the patient's overall condition
Severe air leak syndrome
Immediate cardiorespiratory collapse

Practical applications in trauma patients

Traditionally, trauma patients have been excluded from ECMO consideration due to a high bleeding risk. But given the previously described technological advances, the bleeding profile has significantly improved. Further, many centers are continuously pushing the envelope to minimize anti-coagulation ranges. In select cases, patients may be initiated on a heparin-free protocol for several days where there is a risk of ongoing hemorrhage. This may be especially true in the polytrauma patient who has both a severe traumatic brain injury and a severe ARDS. Muellenbach reported on three patients with such a scenario (intracranial hemorrhage, solid organ injury, and ARDS) [17]. Once active hemorrhage was controlled, the patients were placed on ECMO for pulmonary support without heparin from 1 to 5 days. After anti-coagulation was permissible, a low-level target was selected (aPTT 40–50 s) without reported major complications. Our center uses a similar protocol with a period of anti-coagulation-free ECMO until such time that the brain injury is considered stable.

Additional experience for ECMO in the traumatically injured patient comes from recent military conflict. Bein et al. initially reported on the care of ten US casualties who were supported by a transportable ECLS system [18]. Nine of the 10 patients were successfully weaned from support with one dying of progressive multiple organ failure. Additional supporting evidence for ECMO in traumatically injured patients includes a case series of 52 trauma patients [19]. This cohort had a 15 % cannula complication rate and an impressive 79 % survival, out-performing the expected by mortality based on injury severity scoring.

When comparing ECMO and conventional therapy in the trauma population, there is a signal for improved outcomes using early ECMO. A recent propensity score-matched cohort study comparing ECMO versus conventional ventilator therapy demonstrated a survival advantage for ECMO [20]. With 17 patients in each arm, ECMO was associated with a significant survival advantage (65 vs. 24 %, $p = 0.01$). However, there was a tradeoff in complications, with the ECMO group having more bleeding complications and the conventional group having more pulmonary complications. In this patient population, a practical approach to ECMO consideration is a PaO_2/FiO_2 $\leq$80 with an FiO_2 $\geq$0.9 in the absence of cardiogenic pulmonary edema. This, in addition to a Murray Lung Injury Score $\geq$3.0, supports consideration of ECMO due to a predicted mortality of greater than 80 %.

One often discussed issue is antibiotic use while on ECMO. The guiding principle should be directed at known pathogens. Based on registry data, the rate of nosocomial infections on ECMO is relatively common (VA 37 & VV 27

Table 4 ECMO exclusion criteria

Veno-arterial support Absolute	Veno-venous support Relative
Unrecoverable heart and not a transplant candidate	Mechanical ventilation at high settings >7 days
Chronic organ dysfunction (e.g., ESLD, ESRD)	Recent or worsening CNS hemorrhage
Terminal malignancy	Unrecoverable co-morbid conditions
Aortic dissection	Terminal malignancy
Severe aortic valve disease	Advanced age
Severe peripheral vascular disease	Severe immunosuppression (e.g., ANC <400 mm^3)
	Inability to anti-coagulate
Relative	
Advanced age	
Morbid obesity	
Inability to anti-coagulate	
Systemic infection	
Severe neurological dysfunction	
Non-compliance of medical care	

infections per 1000 ECMO days) [21]. Infection risk appears dose dependent with the lowest rates among those requiring <1 week of therapy. The most common adult pathogens are candida and pseudomonas species, but center-specific antibiograms should be used for optimal treatment. Although periprocedural antibiotics have a role, unless there is an active infection, suppressive antibiotics are not indicated.

Given the critical illness of this patient population, more than 75 % of patients may present with or develop an acute kidney injury [22, 23]. It is not usual for an ECMO candidate to already be at high risk due to sepsis, vasopressor use, and diminished organ perfusion. More than half of these patients will require renal replacement therapy. It is also not uncommon that with volume loading during pre-ECMO resuscitation, these patients may be significantly volume overloaded. Once on organ support, the use of renal replacement therapy is a safe way to manage volume status. There are several ways to perform this, either by use of a percutaneous dialysis catheter distal to the ECMO circuit, placing a hemodialysis filter in-line with the circuit, or connecting a CRRT machine to the ECMO circuit. Several CRRT machines now have software that can monitor and synchronize with pressure changes generated from the ECMO circuit.

Current and future states for ECMO in high-risk surgical Patients

Since 2009, adult ECMO centers have been opening at nearly an exponential rate. These include academic and non-academic centers, in both surgical and non-surgical units. Based on the ELSO international summary, in 2015 there were almost 300 centers worldwide performing more than 6000 cases. Of these, there were more than 1500 adult cases for respiratory failure with a 57 % survival and an average of 11 days of therapy. This was consistent in both trauma and non-trauma patients [24]. There were almost 1800 adult cardiac cases with the most common diagnosis being cardiogenic shock and an average run of 6 days. ECMO therapy survival rates for respiratory and cardiac support are 66 and 56 %, respectively. As previously described, cannulation is now preferentially performed outside of the operating room at the patient's bedside. Further, non-surgeon intensivist placement with seldinger technique has yielded excellent results. Conrad recently published on 190 cannulations and 100 patients, of which 76 were adults. There were only two major cannulation complications, with an overall success rate of 98 % [25].

Looking ahead, innovative indications with active areas of clinical research include E-CPR for both in-hospital and out-of-hospital cardiac arrest, organ donor support in DCD, hypothermic arrest with ECMO-supported reanimation, and minimally invasive extracorporeal CO_2 removal ($ECCO_2R$) for severe hypercapnia. Continued technology refinement should be expected, to include mobile device options and improvements in percutaneous access. Based on this growing area of critical care, we are likely on the cusp of the third-generation of ECLS.

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