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Extra-corporeal Circulatory Support: A Resurgence of a Life Saving Therapy in the Digital Information Age

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Abstract

Extra-corporeal membrane oxygenation represents an evolving therapeutic tool for the treatment of acute severe cardiac and respiratory failure in patients failing maximal medical therapy. Advances in technology along, increasing worldwide clinical successes, and broadening applications have encouraged renewed interest in what was previously considered a salvage intervention associated with poor outcomes. Hopefully, the use of digital media and timely on-line access to scientific advances will allow clinicians and patients who depend on ECMO for survival to benefit in a field in which there is clearly room for improvement in outcomes and understanding. The goal of this Editorial is to provide a brief introduction to the clinical applications, challenges, and limitation of extra-corporeal support.

The hope that vehicles such as this Journal will assist in pushing the frontiers of this technology in a manner in which even small, but rapidly disseminated, advances can have a large impact on patient survival.

Introduction

The evolution of mechanical circulatory support, particularly extra-corporeal therapies, has changed dramatically over the past couple of years. This evolution has coincided with the growth of open-access electronic distribution of scientific literature. Historically, extra-corporeal circulatory support, often with in-line membrane oxygenation (ECMO), has been a niche therapeutic intervention performed only at specialized centers with vast expertise in cardiovascular surgical technology. Initial outcomes with ECMO were discouraging with limited growth and development. Once attempted medical advances face setbacks, their fates are often forever linked to initial poor outcomes. However, as the tools and technology have developed, there has been a renewed interest in ECMO the past 10 years, especially since the H1N1 epidemic. Outcomes have gotten better. Exciting, innovative and life saving applications have been described. Likewise, the explosive growth of the Internet, digital media, and the electronic distribution of ideas and news appears to be ideally matched to help promote the rapid growth of ECMO by assisting in spreading the news of successes, as well as failures. The goal of this review is to describe the current status of ECMO support, outline various ideas for further research and development, and illustrate the role of digital media in this promoting this rapidly advancing technology.

Background

Extra-corporeal membrane oxygenation (ECMO), or extra-corporeal life support (ECLS) in many respects is similar to the cardiopulmonary bypass (CPB) technology that is used worldwide thousands of times daily in the OR for cardiac surgery. Such technology has enabled advances in surgery and outcomes for coronary artery bypass, valve replacement, and more extensive operations involving the aorta and great vessels. In contrast to the intra-operative applications of CPB facilitating the surgical management of cardiovascular path physiology, the intent of ECMO is to support a patient's physiology for a prolonged period of time, often days and weeks (occasionally months) to allow for pulmonary and/or cardiac recovery after an acute insult. In some clinical situations, ECMO allows for temporary supportive means to minimize end-organ damage while bridging to the next clinical decision such as heart or lung transplantation.

A fundamental difference between ECMO and intra-operative CPB applications is incorporation of a blood reservoir in OR CPB circuits. This reservoir allows for the temporary and dynamic storage of blood that can be actively added or removed from the patient's circulation to assist in supporting stable hemodynamic. Due to the level of anticoagulation required to maintain a reservoir with exposure to air, ECMO circuits do not contain this reservoir and this allows a lower degree of anticoagulation without the risk of systemic embolization. Therefore, when volume resuscitation is needed, it is supplemented in a conventional manner via central or peripheral intravenous access. Volume removal requires either diuresis or mechanical removal using ultra filtration technology. Similar to a CPB circuit, heating and cooling systems incorporated into the circuit allow for active patient warming (for treating hypothermia) or cooling (for neuroprotection following cardiopulmonary arrest).

While operative CPB merely replaces the heart and lungs during surgery, ECMO has two fundamental applications and goals of therapy: 1) to support acute respiratory failure and 2) to support acute cardiac failure (often in the context of associated respiratory failure). Despite these two very different applications, the ECMO circuit performs similar tasks. The blood is drained from the body, actively pumped through an artificial membrane that oxygenates the blood while simultaneously removing carbon dioxide (CO_2), and then finally returns the blood back to the patient. Quite simply, 'blue' blood is drained from the patient, converted to 'red' blood and returned back to the patient. However, the manner of vascular access connection will determine the ability to support either of the applications.

Vascular access

Extra-corporeal support is implemented as indicated by the primary goals of support and any acute clinical circumstances. Support of the lung in the context of respiratory failure is often easier to implement than support for cardiac failure. Pulmonary-only

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support, or veno-venous ECMO (VV-ECMO), requires only venous access (no arterial access is required). Venous blood is drained from the patient, oxygenated, cleared of CO_2, and returned back into the venous circulation. Typically, venous access is peripheral and often percutaneous with options including the femoral vein(s), internal jugulars, and less commonly, the subclavian but can be obtained in a variety of ways (See Table 1). Independent of a percutaneous or cut-down approach, the Seldinger technique is employed to advance large-bore cannulas (15-25 French) into the venous system. The placement of these large cannulas is often facilitated by ultrasound guidance. Additionally, the site of access is often dictated not only by the needs of the patient, but also the clinical circumstances and urgency. At our institution, VV-ECMO is typically implemented via both femoral veins. A drainage or outflow catheter is positioned just above the confluence of the iliac veins and the inferior vena cava with the umbilicus as a reasonable external anatomical landmark that can be used to guide placement until proper positioning can be confirmed radiographically (Figure 1). The inflow cannula is then usually positioned into the right atrium with the nipple-line as a landmark until position can be confirmed with a chest x-ray (Figure 2). Using this configuration, venous blood is drained from the abdomen and both lower extremities, and oxygenated blood is returned directly to the right atrium where it then enters the heart, lungs, and ultimately pumped back into the systemic circulation. Of course, the Achilles heel is the assumption that cardiac function is preserved to maintain cardiac output. Patients who are severely hypoxemic, hypercarbic, and/or acidotic might have pulmonary artery vasoconstriction and subsequently acute right heart dysfunction. This can typically be managed during the acute phase medically with inotropes or inhaled vasodilators such as nitric oxide or epoprostenol – however, supportive data and guidelines are lacking. Drainage of only one leg may result in significant shunting of the venous blood from the undrained leg into the native circulation. If the outflow cannula is too high in the vena cava, such as at the level of the hepatic veins, then recirculation and significant hemolysis may result. This means that freshly oxygenated blood that is being returned back into the patient might be overly 'sucked' back into the closely placed out-flow cannula and thereby reducing the efficiency of the entire system. Finally, the deoxyengated and hypercarbic venous blood of the head and arms is inherently mixed and efficiency of the system is reduced. Single cannula technology has been developed to assist in some of these limitations, but this also has limitations [1]. The single cannula approach is considered more technically challenging to place and often requires ultrasound or fluoroscopic guidance to insure the inflow jet is directed across the tricuspid valve. A concern about this cannula (and smaller cannulas in general) is that flow through the smaller lumen results in increased fluid pressures and this can increase the risk of hemolysis. Nevertheless, easier, safer, and more efficient cannulation options represent an exciting area of development and research.

Veno-Venous Inflow Cannula	Veno-Venous Outflow Cannula
Left Femoral Vein Right Femoral Vein Left Internal Jugular Vein Right Internal Jugular Vein Right Axillary Vein	Left Femoral Vein Right Femoral Vein Left Internal Jugular Vein Right Internal Jugular Vein Right Atrium Right Axillary Vein
Veno-Arterial Inflow Cannula	Veno- Arterial Outflow Cannula
Left Femoral Vein Right Femoral Vein Left Internal Jugular Vein Right Internal Jugular Vein Right Atrium Right Axillary Vein	Aorta Right Carotid Artery Right Axillary Artery Left Femoral Artery Right Femoral Artery

Table 1: Vascular Access.

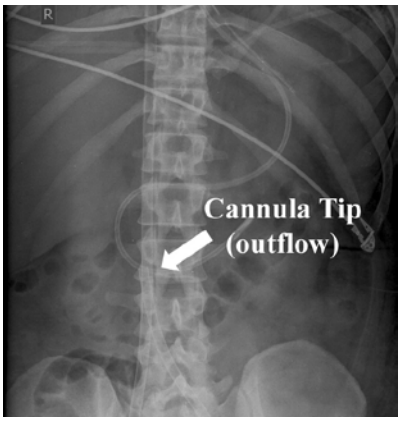

Figure 1: Abdominal x-ray with venous drainage cannula position ideally in the inferior vena cava just above the bifurcation of both iliac veins.

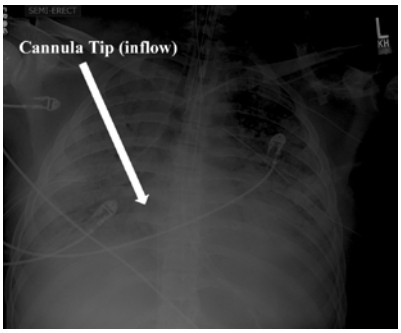

Figure 2: Chest x-ray in a patient with severe respiratory failure with the inflow cannula positioned in the inferior vena cava just at the level of the right atrium.

Cardiopulmonary support via veno-arterial (VA-ECMO) is often more complex to implement and manage. Venous drainage is similar to VV-ECMO, however, the oxygenated blood is returned to the arterial system in a manner that bypasses the heart. Cannulation is performed either percutaneously or by surgical cut-down and either peripheral or central (Table 1). Central access is often performed at the time of cardiac surgery in the context of an inability to wean from cardio-pulmonary bypass. Opening the chest for ECMO cannulation should be discouraged and is often contraindicated for a variety of technical, infectious and other medical reasons. Central arterial inflow is directly into the ascending aorta with techniques that are similar to conventional intra-operative CPB. While percutaneous access is appealing, severe peripheral vasoconstriction secondary to cardiogenic shock can make it technically difficult and increase risks of significant arterial injuries. Femoral artery cannulation, the site most commonly used, drains venous blood from the femoral vein and provides inflow of oxygenated blood in retrograde fashion up through the femoral artery into the aorta. Use of this manner of cannulation often requires placement of a distal perfusion cannula to provide adequate oxygenated blood flow to the leg. If distal flow is not restored promptly, then there is a significant risk for limb ischemia and/or loss. Adequate outflow to the lower extremity can be achieved with either with a small cannula (i.e. a 6 French introducer in the common femoral or superficial femoral artery) or a separate cut-down and cannulation directly into the tibial vessels. A significant downside to femoral access is the mixing that occurs with the blood that is ejected from the heart with the most oxygenated blood furthest away from the

heart and brain. If the heart is still ejecting, any residual undrained blood that passes through the cardiopulmonary tree is usually not well oxygenated and therefore mixed with the oxygenated inflow from the ECMO circuit. More importantly, excessive ECMO inflow increases resistance against the aortic valve thus impeding cardiac output and increasing stagnation of blood within the heart thus creating obvious risks of intraventricular thrombus. For such reasons it is important to ensure that aortic valve opens on at least every second or third beat. Additional concerns are that VA-ECMO may lead to ventricular distention, increased myocardial work and inherently compromise cardiac unloading, rest, and recovery. Furthermore, in patients with significant aortic arteriosclerotic disease, high-pressure distal-inflow from the ECMO inflow cannula may result in systemic embolization and catastrophic strokes.

The other major site of arterial access is the axillary artery. The approach is similar to cannulation for aortic surgery with a small incision inferior to the right clavicle and a side graft is sewn onto the axillary artery as it passes under the subclavian vein and brachial plexus. Although this requires an OR environment and can be technically demanding, axillary cannulation returns maximally oxygenated blood as close as possible to the coronary arteries and the brain without requiring a sternotomy. Carotid artery access, a popular site in children is rarely, if ever, used in adults. The reasons for this are not clear, but likely include concerns stroke, access, and risk for local and technical complications.

Pump and oxygenator technology

The other main components of the ECMO circuit include the oxygenator and the pump. The patient's blood is drained from the outflow cannula, enters the pump, driven through the oxygenator, and finally pumped via the inflow cannula back into the patient. The ECMO circuit has three primary modifiable settings that are 1) the pump speed, which determines the flow of blood through the circuit; 2) sweep that determines the level of carbon dioxide removal from the circuit; and 3) FiO_2 setting, much like the ventilator, is the amount of oxygen supplementation to the blood passing through the circuit. Computer based monitoring systems are used to control flows and driveline pressures (Figure 4) with gas regulators to adjust oxygen support and carbon dioxide removal (Figure 5).

There are three classical types of pumps that are used in ECMO circuits; roller, centrifugal, and axial. Of these three types, the primary style used for ECMO is the centrifugal pump. There are several varieties of centrifugal pumps currently available. Some pumps are driven by external motors like propellers on a submarine. As the motor spins, blood is actively pumped in a continuous non-pulsatile manner. A major drawback is the heat generated from friction, leading to hemolysis and in extreme cases can melt the plastic housing of the centrifugal pump near the axis. While catastrophic failure is rare, exposing the blood to external surfaces can lead to infection. The other type of centrifugal pump is a magnetic levitation pump. As the name suggests, the rotors or fins within the pump housing are connected to a magnet that is suspended within a magnetic field (Figure 3). Because there is no direct contact of the fins with pump housing the amount of friction and heat generated is minimal. These pumps tend to cause less hemolysis. All styles of centrifugal pump are both preload and after load sensitive. Therefore, if there is a downstream occlusion of the pump circuit (after load increase), the centrifugal pump will continue to spin but will not move blood volume forward. Likewise, if there is a reduction in available drainage/inflow volume or any occlusion of the inflow cannula, the pump will suck down on the tubing and generate

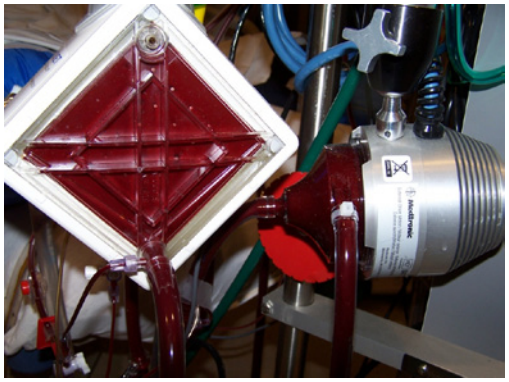

Figure 3: Picture of oxygenator (left, diamond shaped structure) and axial flow pump (right)

Figure 4: Control monitor to adjust flows and to monitor cannula inflow/outflow pressures.

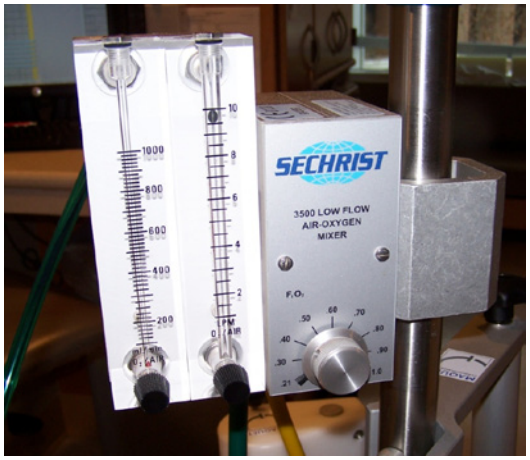

Figure 5: Gas blender (left) to control "sweep" to eliminate carbon dioxide (CO2) and to adjust oxygen support (right).

significant negative pressures that will result in hemolysis. This event is typically referred to as "chugging" or "chatter." Reducing the pump flow/speed will decrease or eliminate this process and allow you time to troubleshoot the cause. If necessary, volume should be given and the pump returned to previous settings.

Roller pumps are limited in their use because of their nature of operation. For roller pumps, tubing is laid in a semicircular raceway where two arms with rollers on the ends rotate at set speeds. As the rollers make contact with the tubing, they depress the tubing and push the blood within the tubing forward. As one roller finishes moving through the semicircular raceway the next makes contact and starts the process over. The problem with roller pumps is that the prolonged and repeated compression of the tubing can cause the tubing to weaken and break down. This can lead to particles being released into the blood stream and embolization, and even tubing rupture, leading to exsanguinations of the patient. Roller pump technology is also more traumatic to the blood and associated with more hemolysis and activation of inflammatory markers and cytokines. Finally, the roller pump is not after load dependent so an occlusion beyond the pump could lead to catastrophic tubing rupture unless limited by a pressure-alarm potentiated system.

Ventilator management

The primary strategy of VV-ECMO ventilator management is to "rest the lungs" until the underlying process is resolved and prevent ventilator-induced barotrauma to the lungs. With an artificial membrane returning highly oxygenated, hyperventilated blood to the inferior vena cava, the settings on the mechanical ventilator can be adjusted to minimize the potential for ventilator induced lung injury [2]. A common goal is to keep lung plateau pressures (Pplat) no higher than 25-28 cm H_2O while maximizing recruitment of the functional residual capacity. Our strategy for accomplishing this includes pressure-control ventilation with inverse ratio ventilation to maximize alveolar recruitment and low mandatory rates of breaths to minimize decruitment. Alternatively, high frequency oscillatory ventilation (HFOV) can also achieve similar goals. Inspired concentrations of oxygen from the ventilator can be reduced to $\leq$ 50% to prevent oxygen toxicity. Additionally, ICU staff should avoid the temptation of increasing these settings despite an abnormal peripheral arterial blood gas. During the acute injury phase of acute respiratory distress syndrome (ARDS), patients will have very low tidal volumes with essentially only dead-space ventilation due to minimal compliance. As compliance and native lung function improve, clinicians may notice that changes in ventilator settings actually impact arterial blood gasses. A daily brief increase in ventilator FiO_2 can be used to test native lung function and indicate lung recovery [3]. A true test of lung recovery can be performed by optimizing ventilator support, turning down the gas source from the oxygenator membrane, and sampling an arterial blood gas 30-60 minutes later. This should be attempted only after the underlying process is perceived to be resolved and the pump speed and sweep flow through the oxygenator have been weaned to minimum settings.

In addition to the ventilator-based therapies of acute respiratory distress syndrome, the clinician should continue evidence-based pharmacologic therapies of ARDS. Standard therapy employed at our institution includes the use of nutritional therapy with enteral nutrition fortified with eicosapentaenoic acid and gamma-linolenic acid [4]. Consideration is also given to the steroid therapy if the duration of acute lung injury is less than seven days and short-term neuromuscular blockade therapy for patient with early ARDS [5]. General critical care practices must also be vigilantly followed to prevent venous thromboembolic disease and gastrointestinal bleeds.

Mechanical ventilator practices for VA-ECMO are also poorly understood with few, if any, guidelines. The primary goal is to achieve normal pulmonary vein saturation that will provide oxygenated blood flow to the coronary circulation without causing ventilator-induced lung injury. Normal lung function in a VA-ECMO patient makes this easily achieved. These patients can be placed on synchronous settings or even extubated to reduce the risk of ventilator-associated pneumonia.

Indications for use

In general, the indications for VV-ECMO are respiratory failure with worsening hypoxemia and/or hypercarbia refractory to maximal medical and ventilator therapy due to a reversible etiology. It should not be viewed as a strategy for patients with severe or end-stage chronic lung disease (see contraindications). Although strict indications are poorly defined, the Murray Score—a validated method of evaluating ARDS severity [6]-was the method in which patients were enrolled in the recent CESAR trial comparing ECMO to ventilator management (Table 2). Unfortunately, because indications are based upon physiologic parameters rather than specific disease conditions, it is not until patients deteriorate hemodynamically that ECMO is considered as a salvage intervention. Furthermore, while guidelines are used to drive therapy, there are little criteria that consider the cause of respiratory failure into the decision to consider ECMO. In general, regardless of the precipitating etiology, a fundamental principle is that the respiratory failure must be secondary to a reversible cause and with appropriate therapy, recovery can occur (Table 3) [7]. Unlike other forms of mechanical support (i.e. ventricular assist devices or even dialysis), VV-ECMO is typically not an option to stabilize patients prior to lung transplantation. While considered extremely high-risk and appropriate in selected patients, lung (or heart-lung) might be an option – but successful outcomes are rare [8].

Similarly, acute cardiac or cardiopulmonary injury indications are based upon specific clinical criteria (Table 4) – often independent of the precipitating cause. In general, VA-ECMO should be considered in patients with acute and potentially reversible actual cardiac injury in which myocardial recovery is a reasonable expectation. Indications are medically-refractory cardiogenic shock as a consequence from a primary event, such as an acute myocardial infarction or acute myocarditis with evidence of end-organ dysfunction/failure. Unlike VV-ECMO, VA-ECMO may serve as a "bridge" to either long-term mechanical assist devices (i.e. left ventricular assist devices) or heart transplantation. While ECMO might be an option for patient in acute heart failure awaiting transplantation, this treatment algorithm requires significant clinical experience and judgment with regards to proper patient management and selection.

Variables:	0	1	2	3	4
PaO_2/FIO_2 (on 100% O_2 for >20 minutes)	≥300	225-299	175-224	100-174	<100
PEEP	≤5	6-8	9-11	12-14	≥15
CXR (# of quadrants infiltrated)	0 (normal)	1	2	3	4
Compliance (ml/cmH_2O)*	≥80	60-79	40-59	20-39	≤19

*The compliance may be calculated as follows: TV /(PIP-PEEP)
The Murray score is calculated by taking the score for each variable and an average score >3 can be an indication for VV-ECMO
Adapted from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988 Sep;138(3):720-3.

Table 2: Indications for ECMO: Respiratory Failure (Murray Score).

Primary	
	Pneumonia
	Bacterial
	Viral
	Fungal
	Aspiration
	Atypical
	Vasculitis
	BOOP (high risk)
	Post-treatment pulmonary embolism
	Pulmonary hemorrhage
	Chemical pneumonitis
Secondary	
	Trauma (Contusion)
	Sepsis/Septic Shock
	Post-Cardiac/Thoracic surgery
	Lung transplant (graft failure/rejection)
	Pancreatitis,
	Other

Table 3: Causes of Respiratory Failure in which ECMO May Be Considered.

- NO surgically correctable cause
- Cardiac Index < 2.2 L/min/m2
- Systolic Blood Pressure < 90 mmHg
- Left Ventricular End-diastolic Pressure ("Wedge") > 20 mmHg
- >2 different high dose inotropes
- Cardiogenic shock despite intra-aortic balloon pump
- Unable to wean from cardiopulmonary bypass

Table 4: Indications for ECMO: Cardiac Failure.

Contraindications

Contraindications for either VV-ECMO or VA-ECMO are similar [9]. Futility of care, a vague concept, or inability to anticoagulate are strict contraindications. More commonly agreed upon patients in whom ECMO would include patients suffering from severe and often irreversible acute or chronic medical problems such as end-stage or metastatic cancers, advanced age, and prolonged or profound neurologic injury. Prolonged periods of cardiopulmonary arrest, in the absence of adequate documented CPR and/or adequate oxygenation (>15-20 minutes) or prolonged periods of end-organ damage prior to initiating therapy are often contra-indications. In a small series, 5 days of mechanical ventilation was associated with 50% mortality, however this increased to 90% mortality at 12 days prior to initiating ECMO [10]. Likewise, untreated or uncorrected surgical or anatomical problems contraindicate ECMO – unless such therapy can assist in stabilizing a patient to assist in adequately fixing such problems. Comorbidities associated with poor outcomes include chronic immunosuppressant, un-grafted burns, bone marrow transplant, intracranial hemorrhage, and known hypercoagulable states [11]. Recent evidence suggests that morbid obesity may reflect a relative contraindication with considerations to the challenges of caring for these patients (such as pressure ulcers, cannula compression/obstruction, etc.) rather than specifics issues related to extra-corporeal support [21]. Pre-ECMO predictors of poor outcomes include: metabolic acidosis (pH<7.1), use of neuromuscular blockade, need for high doses of inotropes/vasoactive drugs and morbid obesity. In general, many contraindications are relative and illustrate the importance of center experience and the need to evaluate each patient critically in terms of associated contributing co-morbidities.

Outcomes

While the first ECMO patient, Esperanza, is still alive 34 years later, ECMO has had a dark history with initial attempts at widespread clinical application being uniformly poor. Coinciding with the rapid development and successes of cardiac surgery during the 1960's and 1970's, there were early attempts at supporting patients long-term with the similar CPB technology that was routinely and successfully used in the OR. Isolated and often dramatic success stories prompted much enthusiasm for broader use in the critically ill for patients suffering and dying from decompensated cardio-respiratory failure. Such enthusiasm eventually prompted a national study sponsored by the National Institutes of Health from 1974 to 1977 [12]. Unfortunately, outcomes were horrible with a <15% survival rate, and the NIH trial was abandoned. For years, many considered ECMO as a failed therapy with little potential for clinical benefit [13]. As with many areas of medicine, and cardiovascular surgery in particular, early failures only fueled a more aggressive pursuit of trying to better understand the complex path physiology, technical limitations and barriers to success. For many years, ECMO research, development and clinical application were limited to only a handful of innovative and high-volume centers – often with small groups of individuals championing a therapy that they had witnessed first-hand in saving the "unsalvageable."

With renewed interest, Mascheroni and colleagues reported in 1986 a 49% (21 patients) survival in patients treated with ECMO for primarily CO_2 removal. The University of Michigan, under the guidance and vision of pioneer Robert Bartlett, reported in their landmark paper a 50% (for pneumonia) to 61% (ARDS) survival in 146 patients treated with VV-ECMO[14,15]. Despite greater than ten years of experience, this survival still reflects the standard in outcomes. A more recent report by the Extracorporeal Life Support Organization (ELSO) reviewed the outcomes in 1473 patients supported with ECMO between 2002 and 2006 [16]. In the 78% of patients supported with VV-ECMO, survival to discharge was 50% and a series of predictors of adverse outcomes were identified (Table 5).

Outcomes for cardiac support, VA-ECMO, have always been worse. Many of these patients sustained massive cardiac failure, either secondary to myocardial infarctions or inability to wean from cardiopulmonary bypass in the OR due to a variety of causes. In such cases, the combined insults of cardiac and respiratory failure, and potential surgical complications thus presenting considerable challenges to successfully manage. Bartlett and colleagues [14] reported a 33% survival in VA-ECMO supported patients. It was realized a rate limiting step to survival was the extensive, and often irreversible, cardiac damage that precipitated ECMO. For example, Rastan and colleagues [15] recently reported in 517 adults supported on ECMO for post-cardiotomy shock. While 63% were successfully weaned from ECMO, only 25% were ultimately discharged from the hospital. In this group, complications on ECMO were common, and often severe (stroke, bleeding) and unresolved acidosis was a common theme in predicting poor outcomes. For patients in whom ECMO served as a bridge to either long-term mechanical support or heart transplantation, the Cleveland Clinic reports a 38% short term [17] and 24% five year survival [18]– suggesting that patients who survival their initial hospitalization (regardless of ECMO indications or therapies used, i.e. transplant) have a reasonable long-term prognosis.

For non-cardiac surgery patients, ECMO has also demonstrated value in supporting high-risk percutaneous coronary interventions in the setting of acute myocardial infarctions. Experiences with this indication is limited to small series [19], although a larger single center series reported a 2-fold increase in survival in patients

Pre-ECMO	
	Increasing Age
	Low body weight
	Duration of ventilator support prior to ECMO
	pH<7.18
	Hispanic/Asian race
	$PaCO_2$ > 70 mmHg
Complications while on ECMO	
	Circuit/pump complications (rupture)
	Stroke/seizures
	Gastrointestinal bleeding
	Pulmonary hemorrhage
	Use of or need for neuromuscular blockage
	pH<7.2 or pH>7.6
	CPR on ECMO[1]
	Inotropic medications
	New infections
	Arrhythmias

Adapted from Brogan TV, et al. Intensive Care Med. 2009 Dec;35(12):2105-14)

[1]Interestingly, cardiac arrest prior to ECMO was not associated with a significantly worse outcome in the univariate model analysis (p=0.28)

Table 5: Predictors of Poor Outcomes of ECMO Support.

presenting with an acute myocardial infarction complicated by severe cardiogenic shock. Sheu [20] argued that ECMO allowed for a more complete revascularization and prevention of acute end-organ damage. Interestingly, this study was not performed in a Ventricular Assist Device/Transplant center and predictors of poor outcomes included post-ECMO heart failure implying the ability to improve on their results had they had access to long-term cardiac support therapies.

While there continues to be isolated reports and cases series building on these experiences, it is clear that there is still much to learn and understand in the pursuit of better short and long-term outcomes. Of significant importance is the speed and efficiency in which advances and failures get disseminated to be universally available to the multi-disciplinary community involved in the care of these patients – this is the potential role for electronic peer-reviewed Journals and other form of digital media and communication tools.

Areas of research

ECMO, despite growing success during the early 21th century, came to the forefront of the medical literature and the world in 2009. This is in part due to the rapid dissemination of information over the Internet in late 2009. As the world was dealing with the consequences of pandemic influenza H1N1 and its associated high mortality, particularly in otherwise young and healthy patients, there were high-profile reports of the successful use of ECMO in catastrophic cases of H1N1 [21-23]. Unrelated to the H1N1 pandemic, the results of the CESAR Trial – a randomized trial comparing ECMO to conventional ventilator management in patients with severe respiratory failure – were published in The Lancet [22]. The primary findings demonstrated a trend towards improved survival, neurologic outcomes and lower costs in patients supported with ECMO versus conventional ventilator management. These mainstream and high-profile publications not only brought the dramatic potential for ECMO to light again, but also highlighted some of the shortcomings, particularly with outcomes that many believe can always be better. The recent development of a portable, easy to use, low-cost, device designed for short-term circulatory support has contributed to a renewed interest in offering ECMO support (Figure 6). While ECMO support is currently only offered at a limited number major specialized centers, this portable technology allows for easily and timely implementation of therapy in smaller programs. Patients, once stabilized, can then be transferred to reference centers with broader experience in complex, and often salvage, interventions [23]. Hopefully with more clinical success, and easier and safer tools, there will be further growth of this life saving technology. All of this has contributed to a variety of bench-to-bedside topics that clearly need to be explored as ECMO utilization grows. Such topics include, but are obviously not limited to

1) Patient Selection – particularly in defining indications, absolute and relative contraindications and a better understanding of predicting who might benefit from ECMO with emphasis on those clinical conditions, diseases, and presentations that are best suited (or least suited) for support.
2) Medication pharmacokinetics and pharmacodynamics (metabolism, binding, and dosing) in patients on long-term extra-corporeal support with prolonged exposure to artificial large surface area tubing and membrane systems in both adults and children.
3) The role of inhaled pulmonary vasodilators, such as nitric oxide and off-label inhaled epoprostenol to assist in lung recovery and reduction of ischemic-reperfusion injuries.
4) Cytokine activation and role of inflammatory mediators in the pathophysiology of acute lung injury and recovery in the context of extra-corporeal support.
5) Optimization of critical care support initiatives in improving outcomes while reducing complications and costs – such as nutritional support, timing and selection of antibiotics, and anticoagulation management.
6) Optimization and timing of ventilator management and ECMO support and weaning during lung recovery.
7) Cost-benefit analysis considering the high-cost of ECMO support.
8) System and process development and clinical training initiatives to optimize outcomes, minimize complications and reduce costs.
9) The role of Pain and Palliative Care support in the context of a high-risk intervention with a known associated high morbidity and mortality rate.
10) The role of early ECLS in post-cardiac arrest victims as a means

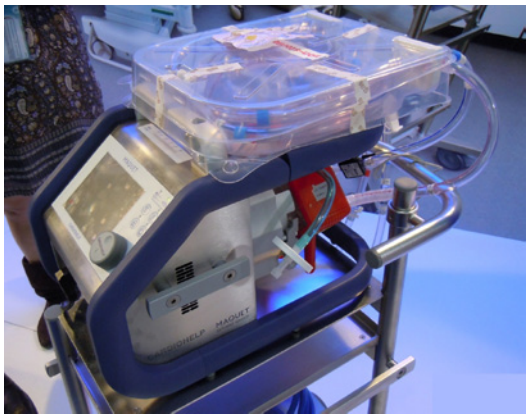

Figure 6: Newly developed, contained, light-weight (~10 kg) portable system for short-term extra-corporeal support (Maquet Cardiovascular LLC, New Jersey USA).

to facilitate induced hypothermia, cardiac rest, and cerebral oxygenation.

While over the years these topics have been the focus of extensive research, with advances in technologies, broader experiences, and better clinical and research tools, clearly there is a need for a better basic understanding of this complex human-machine interaction.

Role of Digital Media, Social Networking, and On-line Access

The rapid expansion and accessibility of the Internet has also played a vital role in the dissemination of medical knowledge. A variety of tools have evolved that have proven invaluable in assisting in the scientific process – particularly in the context of cardiovascular disease management and especially ECMO.

A variety of websites have evolved that have served as digital homes for those looking to join and participate in the ECMO community of health care providers. The most popular is the website for the Extracorporeal Life Support Organization (ELSO) [24]. The ELSO website also serves as the on-line home for the International Registry for ECMO and over 160 member sites. This site also provides links to other sites, educational resources and a list of the extensive and rapidly growing bibliography related to ECMO support. Many participating medical centers also have their own institutional websites that serve as a resource for patients, clinicians and researchers.

Another invaluable on-line tool that has contributed greatly to the resurgence of ECMO is the LISTSERV. LISTSERV (L-Soft International, Inc. Landover, MD) [25] is an internet-based email application, typically hosted by a moderator. It is a real-time means of communicating with colleagues' world-wide by initiating or participating in topics of discussion. LISTSERVs are typically organized around specific topics and invite participants interested in those topics to post topics of interest. Membership is often free and topics can be initiated by any member and distributed to all members for comment. Several LISTSERVs have evolved that serve the needs of the ECMO community. One of the earliest and most active has been the Heart Surgery Forum LISTSERV [26] – although focused on cardiovascular surgery, ECMO is often an active topic of conversation and debate. A similar LISTSERV for the Critical Care community also frequently discusses topics related to ECMO [27]. A LISTSERV dedicated to ECMO is also quite active [28]. LISTSERVs have also been invaluable in nurturing professional collaborative relationships among clinicians and researchers worldwide.

Probably one of the most important contributions to the explosive growth and spread of medical science has been on-line access to the medical literature. The Internet has revolutionized the accessibility of medical literature and the speed in which ideas and research can be distributed. Historically, peer-reviewed science in print form was a process that often took months if not years, for ideas to reach the medical community. As recently as 2000, manuscripts and images were submitted to editors in paper form, copied and distributed to Reviewers. Once the time-consuming peer-review process was complete and the manuscript was published, distribution was limited to a paper format. Access was limited to individuals or institutional subscribers and often at considerable expense. This was a significant roadblock to access and participation to those with limited resources, particularly in developing countries. Over time, more "print" journals made their manuscripts available in a digital format to download. Even the initial peer-review process has become completely digital – a step that has dramatically simplified and expedited the entire review to publication process. The distribution model evolved such that electronic versions were immediately available to subscribers and then after a period of time (typically ~1 year), free access was granted to all.

The latest iteration of digital distribution is where we are now–Open Access Journals. Open Access Journals, such as this one and a similar on-line journal dedicated to mechanical circulatory support [29], are completely digital from submission to publication. By using electronic publishing tools and avoiding the costs of paper distribution, the costs are minimized and distribution is limited only by Internet access capabilities. Unlike traditional print media in which costs are born by advertisers and subscribers, digital open access media expenses are supported by advertising and authors. Authors typically pay a nominal publication fee, and in exchange, immediately after publication, their work is available free of charge worldwide. As "publication" and "distribution" costs have dropped, so has the proliferation of specialty journals. Popular search engines, such as Google Scholar [30] are supplementing more traditional medical search engines, such as PubMed [31] to simplify the search and access process. Never before has it been so easy, fast, efficient and inexpensive to distribute science.

Other Internet social media tools, such was LinkedIn, Twitter and Facebook (just to name a few) have evolved to assist in global real-time communication, collaboration and exchange of ideas. The roles these tools play in advancing science are still in infancy as concerns of privacy, accuracy and integrity of data and personal information. Sites such as Wikipedia [32] expand on the concept of a digital encyclopedia by allowing "expert" volunteers to provide 'content' and update entries in real-time. Inherent in the design are mechanism that attempts to insure accuracy, reliability and source verification. While different than peer-review publication, such online sites (along with countless other sources of medical information – both commercial and non-profit) are valuable starting points when searching for information once one recognizes some of the potential inherent limitations of the data.

What does this mean to provide extra-corporeal life support? While Wikipedia volunteers information serve as a basic online starting point for understanding much more complex concept [33]. Other social media tools often discuss ECMO, the real advantages are the speed and global breadth of ideas and their open exchange. As we learned during the H1N1 Pandemic of 2009, it was digital media dissemination and tools that help spread the recent applicable data. Clinicians and researchers around the world were able to easily share their findings and concerns, as well as to document, prove, and study has worked and equally importantly, what did not. Reports of ECMO for H1N1 were topics of digital conversation weeks before even on-line peer-reviewed reports appeared electronically – and months before paper manuscripts made their way to mailboxes and library shelves. For critical illnesses, such as H1N1, and what used to be obscure life-saving therapies, such as ECMO – the ability to get the word out as fast as possible, in an accurate, peer-reviewed, and "free" model using the Open Access publication model is an invaluable revolutionary advance in medical research.

Conclusions

ECMO is an invaluable tool for the support of acute and severe respiratory or cardiac failure. While simple in theory and application, the technology and science behind supporting patients long-term with extra-corporeal support is complex. There still remains much to learn, particularly as the tools for support continue to rapidly evolve. Even small advanced in application and understanding can have an immediate impact on improving outcomes in patients who would otherwise die.

The ability to rapidly, efficiently, and accurately report the growing knowledge base for ECMO will be a critical component in long-term success and improved survival. Digital media is an invaluable tool for spreading this knowledge to those who need it the most – the clinicians at the bedside of a dying patient.

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