Published in final edited form as:

ASAIO J. 2015 ; 61(1): 2–7. doi:10.1097/MAT.0000000000000150.

Extracorporeal Life Support: Experience with 2000 Patients

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Abstract

This is a review of the University of Michigan experience with extracorporeal life support (ECLS) also known as extracorporeal membrane oxygenation (ECMO). Two thousand patients were managed with ECMO from 1973–2010. The first thousand were reported previously.

Of the 2000 patients, 74% were weaned from ECLS, and 64% survived to hospital discharge. In patients with respiratory failure, survival to hospital discharge was 84% in 799 neonates, 76% in 239 children, and 50% in 353 adults. Survival in patients with cardiac failure was 45% in 361 children, and 38% in 119 adults. ECLS during cardiac arrest (ECPR) was performed in 129 patients, with 41% surviving to discharge. Survival decreased from 74% to 55% between the first and second thousand patients. The most common complication was bleeding at sites other than the head, with an incidence of 39%, and the least frequent complication was pump malfunction, with a 2% incidence. Intracranial bleeding or infarction occurred in 8% of patients, with a 43% survival rate. This is the largest series of ECLS at one institution reported in the world to date. Our experience has shown that ECLS saves lives of moribund patients with acute pulmonary and cardiac failure in all age groups.

Keywords

ECMO; extracorporeal circulation; cardiac failure; respiratory failure

Introduction

Extracorporeal life support (ECLS) also known as extracorporeal membrane oxygenation (ECMO) has been used to treat critically ill patients with respiratory and cardiovascular failure for over four decades. Hill and colleagues published the first successful use of ECLS in 1972 in a trauma patient who developed ARDS.¹ This was followed by the first successful use of ECLS in cardiogenic shock in 1973² and newborn respiratory failure in 1975. Since that time, the use of ECLS has been validated as a life-saving therapy,^{3,4} and

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Conflict of Interest and Source of Funding: The authors claim no conflict of interest or source of funding attributable to this manuscript

centers with expertise in ECLS have grown worldwide through international collaborative efforts. In addition to the dissemination of ECLS around the globe, the indications for ECLS use have expanded over the years from neonatal respiratory failure to its use during cardiac arrest (ECPR).

There have been several large series of ECLS patients reported from centers around the world. Groups from Europe, Asia and Australia have published studies examining a few dozen to several hundred patients at a time.⁴⁻⁷ However, the University of Michigan Hospital, in Ann Arbor, Michigan, has treated the largest number of patients with ECLS the world over. We previously reviewed and presented the results of the first 1000 patients treated with ECLS at the University of Michigan.⁸ The aim of this report is to present the next set of 1000 patients treated with ECLS at the University of Michigan in combination with and in comparison to the first 1000 patients, with a unique perspective on the evolving use of ECLS over the past four decades.

Methods

We reviewed the data on 2000 consecutive patients treated with ECLS by the University of Michigan ECMO team from 1972–2010. The data were collected prospectively at the time of treatment using the Extracorporeal Life Support Organization (ELSO) registry forms and computer database.⁹ There are currently nearly 60,000 cases in the total worldwide ELSO registry. We focused on the differences between the first and second thousand patients to gain a better understanding of our ECLS experience over four decades.

Basic statistics were performed using SPSS version 17 software package (IBM, Chicago, IL), and tests included the t-test for Equality of Means and the Pearson Chi-Square test. Significance was defined as $p < 0.05$.

Results

The first 1000 patients in this group were previously reported in detail by Bartlett and colleagues.⁸ They were treated between 1972 and 1998 (26 years). The second group of patients was treated between 1998 and 2010 (12 years).

Survival by Diagnosis

The ECLS survival was 64%. The growth and distribution of cases is presented in Table 1. Since 1998, the greatest areas of growth in ECLS use have been cardiac failure, adult respiratory failure, and the emergence of ECPR.

The distribution of indications for ECLS use and survival is outlined in Table I. Survival was significantly better in the first thousand patients than those treated after 1998 (74% vs. 55%, $p < 0.01$). Between the first thousand and second thousand patients, the proportion of neonates treated for respiratory failure decreased ($n = 586$ vs. 213), and this group had a significant decrease in survival (88% vs. 72%, $p < 0.01$). The greatest drops in neonatal respiratory survival were seen in the diaphragmatic hernia and “other” groups. The “other” group is defined as those with rare indications that cannot be placed in any of the larger

categories. Median oxygenation Index (OI: $\text{FiO}_2 \times \text{Mean Airway Pressure} \div \text{PaO}_2$) was similar amongst the neonatal respiratory patients in the first and second thousand groups (42 vs. 40, $p=0.62$). OI in survivors was significantly lower than in those who died (48 ± 32 vs. 56 ± 35 , $p=0.02$).

Survival increased in the pediatric respiratory group from 70% to 84% ($p<0.01$), with greatest increases in those with pneumonia and ARDS. Median OI was also similar over time in this group (41 vs. 40, $p=0.53$), and mean OI was again higher in those who died; (42 ± 20 vs. 50 ± 31 , $p=0.05$)

Adults with respiratory failure increased by over 40%. While absolute survival rate in this group was greater after 1998, the difference was not statistically significant (46% vs. 52%, $p=0.33$). The distribution of diagnoses and survival of the adult respiratory group are shown in Table I.

There was a substantial increase in the use of ECLS for cardiac failure in both pediatric and adult patients (136 vs. 344), but survival was nearly identical overall (44% vs. 43%, $p=0.84$). As an adjunct to ECLS for cardiac failure, ECPR emerged since 1998 as a heroic measure to save moribund patients in cardiopulmonary arrest. As of 2010, there were 129 patients in our series, with a 41% survival rate. The incidence and survival in the adult and pediatric populations were nearly identical, as seen in Table I.

The database did not prospectively record the exact cause of death. However, in our experience, most deaths occurred due to lack of improvement of primary disease on ECLS, multi-system organ failure, sepsis, or loss of CNS function.

Patient and ECLS Run Characteristics

There was very little change in pre-ECLS ventilator days in any group, with the neonatal respiratory and adult cardiac groups with the shortest duration and pediatric respiratory group having the longest (Table II). The mean duration of ECLS increased from 5.8 to 7.7 days in neonatal patients, decreased from 12.8 to 8.6 in pediatric patients, and decreased from 10.4 to 7.3 in adult respiratory patients ($p<0.01$ in all groups).

The cannulation mode for ECLS stayed relatively stable in all groups, based on the physiologic derangement specific to each group (Table II). The majority of cardiac and ECPR patients were supported with VA-ECLS, and there was increased usage of the VV mode after 1998 because of the availability of double lumen cannulas for children and adults.

Multiple ECLS runs were conducted in 92 total patients, with 35% survival. Six of these patients were supported with ECLS 3 times, with 17% survival. The most frequent group placed on ECLS multiple times was the pediatric cardiac group ($n=27$), with an overall survival of 26%.

Complications

The most common complication was non-intracranial bleeding, usually associated with cannula insertion sites, in 39% of patients. Renal failure defined as the need for dialysis or hemofiltration was the second most common complication at 31%. The least common complications were pump malfunction (2%), air entry into the circuit (8%), and intracranial bleeding or infarction (8%). The complications associated with the greatest survival were air entry into the circuit (71%) and blood clots in the circuit (62%); those associated with poorest survival were pump malfunction (36%), need for dialysis (38%), and cardiac arrhythmia (39%).

The neonatal respiratory failure group had lower incidence than the other patient groups in all complication categories other than clots in the circuit. Intracranial bleeding occurred in less than 10% of patients in all groups other than the ECPR group. Arrhythmias occurred most frequently in the cardiac failure patients and adults with respiratory failure. New infection while on circuit was most common in the pediatric and adult respiratory patients, and survival was less than 50% in most categories of patients who developed an infection. Mechanical complications were relatively rare. The lowest incidence was pump malfunction, but patients with this complication had particularly poor survival in all but the neonatal and pediatric respiratory groups. There was low incidence of cannula-related complications, and this was associated with variable survival. (Tables III and IV)

Discussion

Our data reveal decreased survival over time, with the only significant increase in survival coming in the pediatric respiratory group. In the first thousand patient group, a large subsection of patients were neonatal respiratory patients with meconium aspiration, infant respiratory distress, and sepsis (40%) who have been shown to have remarkable survival as a result of ECLS treatment (92%).⁹ The use of ECPR in the late 1990s added a new subset of patients with a predisposition towards poorer survival. In our experience, early successes using ECLS have led to increased use in patients who would have historically been too ill for ECLS. This is perhaps the reason for decreased survival in neonatal respiratory patients with diaphragmatic hernia and “other” diagnoses in the second group. Oxygenation Index (OI) is a measure that has been named as a predictor for mortality in neonates and children with respiratory distress.¹⁰ Median pre-ECLS OI was similar between these groups in our study, likely due to the recognized benefit of ECLS once OI reaches 40.

Due to our studies and others,^{3,10} ECLS has become an accepted therapeutic modality for use in treating neonates with respiratory failure, particularly those children with meconium aspiration, respiratory distress, and sepsis. Extracorporeal gas exchange allows time for the lungs to heal from the physiologic insult, resulting in excellent survival that has remained at greater than 90%. Patients with CDH and persistent pulmonary hypertension, however, tend to have greater physiologic derangements at baseline, resulting in more modest survival. In our study, survival slightly decreased over time, likely due to a sicker patient population being placed on ECLS.

Advances in pulmonary treatment modalities such as inhaled nitric oxide (iNO), inhaled surfactant, and high frequency oscillatory ventilation (HFOV) have led to less need for the more invasive ECLS while maintaining equivalent survival.^{11,12} We saw virtually no change in the modality of ECLS, even with the demonstration of efficacy of the venovenous modality and equivalent survival in the neonatal population.^{13,14}

Pediatric respiratory patients had increased survival in the later patient group. Similar to the neonatal group, a survival advantage has been shown with ECLS over conventional treatment in severe respiratory failure.¹⁵ Pre-ECLS factors associated with mortality have included OI, Pediatric Risk of Mortality score (PRISM), PaCO₂, and shock.¹⁵ Patients who died had higher mean OI, representing severity of respiratory failure.

ECLS survival decreased with renal failure (serum Cr >3.0), failure to return the patient to dry weight, and the use of inotropes.¹⁶ Due to these findings, we began to employ the early use of continuous renal replacement therapy (CRRT) for pediatric ECLS patients with signs of renal failure in our treatment algorithm. Patients in the second thousand group who underwent hemodialysis or had elevated serum creatinine had increased survival over renal failure patients in the first thousand. Since 2008 we have decreased sedation which allowed spontaneous breathing,^{17,18} and applied ECMO before salvage status. Along with advances in ECLS technology, these factors have helped to decrease mortality in pediatric respiratory failure patients treated with ECLS.

Other trends over time included increasing use of the venovenous modality, likely due to the advent and efficacy of dual-lumen venous cannulas.¹⁹ Patients spent less time on ECLS, possibly representing the success of multi-modality treatment and decreased pulmonary injury in the pre-ECLS time period.

Despite controversy in the critical care community on the indications for and efficacy of ECLS in adult respiratory failure patients, its use in this population is increasing in frequency. There have been several cohort and case control studies that mostly examined ECLS use in ARDS patients, including one from our group, showing survival to discharge in the 50–66% range.^{20–22} The most robust trial in support of ECLS in the adult respiratory failure group was the CESAR trial from the UK that showed in a prospective randomized multicenter fashion that transfer to care in an ECLS capable center was superior to care at a center without ECLS expertise.⁴

From the first to the second thousand set of ECLS patients, we saw an increasing proportion of adults treated for respiratory failure, and with this came a trend towards increased survival in both the pneumonia and ARDS groups, reflecting patient selection and improving ECLS treatment strategies for the patient as a whole. This improved survival has led to maintaining patients with severe pulmonary failure on ECLS for prolonged durations while awaiting lung recovery. Our group published the account of a patient who survived for 53 days on VV-ECLS after suffering severe ARDS.²³

As in the pediatric respiratory group, we observed decreased ECLS duration and an increasing trend towards the use of VV-ECLS. The standard cannulation mode for adults with respiratory failure is VV-ECLS, and the efficacy of dual-lumen right internal jugular

venous cannulation has encouraged the use of VV-ECLS in practice.^{24–27} VA cannulation in respiratory failure is now reserved for those in refractory shock or concomitant cardiac failure

ECLS for adult respiratory failure came into the international spotlight during the influenza A(H1N1) pandemic of 2009. The pandemic struck first during winter in the Southern Hemisphere, where the Australia and New Zealand (ANZ) ECMO Influenza Investigators published an account of their robust experience using ECLS to treat H1N1 patients.²⁸ The ANZ ECMO group placed 68 patients on ECLS, and had a 71% survival to ICU discharge. The work of the ANZ ECMO group served as a guide for intensivists in the Northern Hemisphere in the mobilization of ECLS teams to prepare for the spread of the H1N1 pandemic in the coming winter. Many groups in Europe, Asia, and the United States published their experience, adding to the worldwide catalogue of ECLS in the face of H1N1 influenza.^{29–32}

Our group saw adult respiratory ECLS cases increase from 6 in 2008 to 24 in 2009. This number regressed to 7 cases in 2010. In the end, this new worldwide fund of knowledge allowed for a greater understanding of the use of ECLS to treat H1N1, use of ECLS in general, and the mobilization of hospital resources to accommodate the sudden demand for ECLS.^{33,34}

The number of pediatric cardiac cases doubled in the second thousand (105 to 256) but the survival stayed the same (48% vs. 44%). Until recently ECLS was the only mechanical life support system for children with profound cardiogenic shock. The main application has been in cardiac failure immediately following cardiac operations, within minutes or hours of coming off cardiopulmonary bypass. In 2013 the pediatric Berlin HeartVAD became available. The FDA qualifying trial for the Berlin Heart was a matched pairs study, matching to the ELSO pediatric cardiac database.³⁵ The number of myocarditis and cardiomyopathy cases increased in the second thousand, as we learned that the survival is quite good in that condition (50% to 60%).

The number of adult cardiac cases doubled in the second thousand cases (31 to 88), and survival increased from 33% to 40%. Unlike pediatric cardiac ECLS, adult patients can proceed to VAD and ultimately transplant. This algorithm has evolved in our center.³⁶ VA ECLS is used as the first mechanical support, at times after failing on intraaortic balloon pump. If CNS function is good and there are no other contraindications, we then proceed to VAD implantation with the intent of chronic support until transplantation.

In the first 1000 patients, VA ECLS was sometimes used for patients who arrested as preparations were underway for cannulation. These cases are counted only as respiratory or cardiac cases. Beginning in 1999 the category of ECPR was instituted to identify patients who were in unexpected cardiac arrest, CPR was underway, and VA ECLS was added as an adjunct to CPR. This occurred rarely, since the circuit must be primed with cannulation possible within a few minutes of onset of CPR. The survival rate is 41%, much better than CPR alone (<10%).³⁷ The survival rate is essentially those patients who regain both cardiac and brain function.

Complications

Major concerns for complications for all patients treated with ECLS continue to revolve around the extremes of the coagulation cascade, manifesting as thrombosis in the circuit, intracranial hemorrhage/infarction, and bleeding. To this end, laboratories have been researching non-thrombogenic surfaces to obviate the need for anticoagulation. These range from heparin-coated circuit surfaces³⁸ to nitric oxide-eluting surfaces.³⁹

Overall Outcome

The decrease in survival rate between the first 1000 patients (74%) and the second thousand (55%) is a reflection of the types of patients and the severity of illness in the two groups. The first 1000 were primarily newborn infants with respiratory failure (88% survival) with little cardiac failure and almost no ECPR. In the second thousand the percent of newborn respiratory failure was 72% and most of those were diaphragmatic hernia patients who have a worse prognosis because of pulmonary hypoplasia. Since 2000 we have expanded ECLS for severe cardiac and pulmonary failure in children and adults. These patients have a worse prognosis than newborns because of the increased incidence of irreversible heart or lung failure. We added ECPR cases that have a high incidence of irreversible brain injury. Concomitant with a raise in the severity of disease has been the steady improvement of the devices, methods of anticoagulation, and better understanding of cardiac and respiratory management on ECLS, leading to 55% survival. There is much room for improvement.

Future

In 2010 we began using the next generation of ECMO devices (so called ECMO2). These devices make ECLS much simpler, safer, more automatic, and decrease the need for anticoagulation. ECLS can be managed by the ICU nursing staff, rather than the continuous attendance of an ECMO specialist. The cost and ease of application are improving. We will see how these changes affect the patient groups and outcome in the next 1000 patients.

Conclusions

Our first 1000 ECLS patients were managed over 26 years and were predominantly newborn respiratory failure who rarely have irreversible injury. The survival rate was 74%. The next 1000 patients we managed over 12 years and the survival rate was 55%. In the second 1000 the indications were expanded to children and adults with cardiac and pulmonary failure including patients in cardiac arrest (ECPR).

ECLS is a mature technology which is used for temporary life support in patients with a high risk of dying (70–80%).^{3,4,8,13,15,17,41} In the last 1000 patients ECLS resulted in 70–80% survival in neonates and children, 50% in adults with respiratory failure, and 40% in patients with cardiac failure.

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Table 1

Survival Outcomes of 2000 Extracorporeal Life Support Patients

	1 st 1000 Patients		2 nd 1000 Patients		P (survival)
	N	Survived to DC/Transfer	N	Survived to DC/Transfer	
Neonatal Respiratory	586	88%	213	72% *	<0.01
Meconium Aspiration	207	98%	51	96%	
Diaphragmatic hernia	83	68%	83	55%	
Infant respiratory distress syndrome	99	89%	8	88%	
Persistent pulmonary hypertension	58	93%	41	83%	
Sepsis	92	84%	5	80%	
Other	47	80%	25	56%	
Pediatric Respiratory	132	70%	107	84% *	<0.01
Pneumonia	73	74%	43	91%	
ARDS	59	61%	18	89%	
Non-ARDS acute respiratory failure	0	n/a	46	78%	
Adult Respiratory (see Table 1b)	146	46%	207	52%	0.33
Pneumonia	77	43%	76	55%	
ARDS	47	43%	70	53%	
Non-ARDS acute respiratory failure	22	64%	61	48%	
Cardiac	136	44%	344	43%	0.84
Pediatric	105	48%	256	44%	
Adult	31	33%	88	40%	
ECPR	0	n/a	129	41%	n/a
Pediatric	0	n/a	66	44%	
Adult	0	n/a	63	40%	
Total	1000	74%	1000	55% *	<0.01

ARDS = acute respiratory distress syndrome, ECPR = extracorporeal cardiopulmonary resuscitation.

* p<0.05 indicates significance.

Table II

Extracorporeal Life Support (ECLS) Run Characteristics in 2000 Patients

	Respiratory Patients				Cardiac Patients				ECPR	
	Neonatal	Pediatric	Adult		Pediatric	Adult			Peds	Adult
	1 st 10 000	2 nd 1 000	1 st 10 00	2 nd 1 000	1 st 10 00	2 nd 1 000	1 st 10 00	2 nd 1 000	1 st 10 000	2 nd 1 000
Pre-ECLS ventilator time (mean days)	1.4	1.2	5.4	6.2	3.5	3.8	3.5	3.8	1.9	4.4
P value	0.22		0.66		0.75		0.79		0.11	
ECLS duration (mean days)	5.8	7.7	12.8	8.6	10.4	7.3	6.8	7.0	4.4	5.8
P value *	<0.01 *		<0.01 *		<0.01		0.76		0.06	
Venoarterial	57%	57%	56%	46%	38%	13%	100%	93%	100%	95%
Venovenous	42%	43%	44%	52%	62%	83%	0%	1%	0%	1%
VA+V	1%	<1%	0%	3%	0%	4%	0%	6%	0%	4%
										22%

Results from patients 1–1000 as reported by Bartlett, et al¹¹ ARDS = acute respiratory distress syndrome, ECPR = extracorporeal cardiopulmonary resuscitation. VA + V = veno-arterial + venous, ECPR = extracorporeal cardiopulmonary resuscitation.

* p<0.05 indicates significance.

Table III

Complications in 2000 Respiratory Extracorporeal Life Support Patients

	Neonatal Respiratory		Pediatric Respiratory		Adult Respiratory	
	1 st 1000 N=586	2 nd 1000 N=213	1 st 1000 N=132	2 nd 1000 N=107	1 st 1000 N=146	2 nd 1000 N=207
Physiological	Incidence (Survival)					
Intracranial bleeding infarction	10% (61%)	9% (63%)	5% (45%)	7% (75%)	8% (9%)	2% (25%)
Other bleeding	17% (81%)	17% (68%)	54% (60%)	41% (71%)	68% (44%)	52% (38%)
Hemolysis	15% (76%)	27% (64%)	11% (21%)	28% (80%)	5% (50%)	9% (22%)
Dialysis/hemofiltration	14% (64%)	15% (70%)	39% (47%)	25% (70%)	43% (35%)	55% (37%)
Creatinine>3 mg/dL	10% (63%)	0	8% (55%)	2% (100%)	28% (37%)	17% (43%)
Arrhythmia	3% (78%)	12% (60%)	11% (47%)	14% (33%)	35% (39%)	28% (36%)
New Infection	4% (50%)	4% (33%)	30% (65%)	20% (76%)	30% (41%)	23% (38%)
Mechanical						
Oxygenator change	7% (63%)	5% (36%)	16% (52%)	9% (80%)	23% (50%)	8% (47%)
Pump malfunction	2% (89%)	<1% (0%)	4% (80%)	1% (100%)	5% (29%)	2% (0%)
Circuit clots	41% (77%)	29% (60%)	2% (0%)	25% (69%)	3% (0%)	25% (38%)
Circuit air	17% (80%)	4% (67%)	0	10% (9%)	0	4% (57%)
Cannula problems	18% (81%)	21% (66%)	20% (44%)	22% (79%)	27% (43%)	16% (35%)

Complications in 2000 ECLS patients separated by type of support. Complication incidence and survival is compared between the first and second 1000 ECLS patients treated at the University of Michigan.

Table IV

Complications in 2000 Cardiac Extracorporeal Life Support Patients

	Pediatric Cardiac		Adult Cardiac		ECPR		Total
	1 st 1000 N=105	2 nd 1000 N=256	1 st 1000 N=31	2 nd 1000 N=88	2 nd 1000 N=128	2 nd 1000 N=2000	
Physiological	Incidence (Survival)						
Intracranial bleeding/infarction	4% (0%)	9% (17%)	3% (0%)	8% (0%)	12% (33%)	8% (43%)	
Other bleeding	64% (36)	53% (38%)	52% (33%)	63% (36%)	45% (38%)	39% (48%)	
Hemolysis	10% (20%)	39% (23%)	10% (0%)	24% (33%)	23% (31%)	19% (47%)	
Dialysis/hemofiltration	38% (40%)	44% (16%)	45% (14%)	45% (33%)	48% (24%)	31% (38%)	
Creatinine >3 mg/dL	4% (0%)	2% (0%)	29% (11%)	19% (47%)	10% (54%)	10% (47%)	
Arrhythmia	28% (48%)	33% (29%)	52% (19%)	47% (27%)	41% (40%)	20% (39%)	
New Infection	15% (50%)	13% (16%)	19% (17%)	13% (27%)	14% (44%)	13% (44%)	
Mechanical							
Oxygenator change	10% (9%)	8% (25%)	10% (33%)	5% (25%)	9% (42%)	9% (47%)	
Pump malfunction	2% (0%)	2% (17%)	6% (50%)	0% (0%)	2% (20%)	2% (36%)	
Circuit clots	5% (80%)	35% (31%)	0	25% (44%)	21% (28%)	26% (62%)	
Circuit air	0	7% (42%)	3% (100%)	3% (0%)	5% (17%)	8% (71%)	
Cannula problems	8% (25%)	9% (35%)	6% (100%)	11%(10%)	14% (17%)	17% (56%)	

Complications in 2000 ECLS patients separated by type of support. Complication incidence and survival is compared between the first and second 1000 ECLS patients treated at the University of Michigan.