Respiratory Support

Outcomes Using Extracorporeal Life Support for Adult Respiratory Failure due to Status Asthmaticus

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Our objective was to describe the outcomes for extracorporeal life support (ECLS) use in adult respiratory failure because of status asthmaticus and to determine whether ECLS use in status asthmaticus is associated with greater survival than other indications for ECLS. This retrospective cohort study used the multicenter, International ECLS Organization Registry. The study population included 1,257 adults with respiratory failure requiring ECLS. Status asthmaticus was the primary indication for ECLS in 24 patients. A total of 83.3% of asthmatics survived to hospital discharge compared with 50.8% of nonasthmatics (n = 1,233) [odds ratio (OR) favoring survival for asthmatics = 4.86, 95% confidence interval (CI) 1.65–14.31, $p = 0.004$]. The survival advantage for asthmatics remained significant after adjustment for potential confounders. Complications were noted in 19 of 24 asthmatics (79.2%). In conclusion, we found that status asthmaticus, as an indication for ECLS in adult respiratory failure, seemed to be associated with greater survival than other indications for ECLS. However, complications are common and whether ECLS confers a survival advantage compared with other salvage treatment options remains unknown. More detailed information and complete reporting of ECLS use for status asthmaticus are needed to determine whether and when the potentially life-saving intervention of ECLS should be initiated in the asthmatic failing conventional therapy. *ASAIO Journal* 2009; 55:47–52.

Extracorporeal life support (ECLS) has been used as salvage therapy for adults with acute respiratory failure since 1972.[1] Previous randomized controlled trials failed to show a survival advantage when ECLS was used in refractory adult respiratory distress syndrome (ARDS).[2,3] A multicenter trial, which focused on more reversible cases of acute respiratory failure, has recently been completed and the investigators reported a survival benefit for ECLS compared with conventional ventilation.[4] Status asthmaticus, a potentially reversible process, represents the type of disease that may benefit from ECLS.

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Asthma exacerbations frequently lead to urgent care visits and hospitalizations and are associated with significant morbidity and mortality in the most severe cases.[5–7] Although several case reports[8–14] and one case series[15] exist describing the successful use of ECLS for near-fatal adult status asthmaticus, it is unknown how often ECLS is actually used for life-threatening status asthmaticus, and an assessment of the outcomes of these patients has not been performed to date.

Using the international Extracorporeal Life Support Organization (ELSO) Registry,[16] we aimed to describe the outcomes for ECLS use in adult respiratory failure because of status asthmaticus and to determine whether ECLS use in status asthmaticus is associated with greater survival than other indications for ECLS. We hypothesized that utilization of ECLS in adult respiratory failure because of status asthmaticus is associated with greater survival than for other ECLS indications. Some of the data in this article was previously reported in abstract form.[14,17]

Materials and Methods

Study Population

This retrospective cohort study, using the ELSO registry, described outcomes in adult acute respiratory failure ECLS cases and compared mortality by etiology for respiratory failure. The ELSO registry is a voluntary database that has reported capturing the vast majority of ECLS cases in the United States and internationally.[18] All adult (≥18 years) acute respiratory failure cases between January 1986 (the inception of the registry) and September 2006 were included in this analysis. All ELSO registry cases are anonymously coded.

The primary outcome was survival to hospital discharge for respiratory ECLS cases. The primary exposure was the primary indication for ECLS; asthmatic *vs.* nonasthmatic respiratory ECLS cases based on primary etiologic diagnosis ascribed to each patient according to the International Classification of Diseases. Given our primary hypothesis, secondary diagnoses were not used to categorize cases as asthmatic or nonasthmatic (*i.e.*, an asthmatic who received ECLS for severe pneumonia was classified as pneumonia); as such, secondary diagnoses were not made available for this analysis. The nonasthmatic cases were grouped by primary diagnosis when there existed ≥20 discrete cases for a given respiratory failure etiology; otherwise, they were classified as "other."

Potential covariates included all data reported voluntarily to ELSO from participating centers: baseline patient demographics; pre-ECLS physiologic and clinical data; and mode of per-

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fusion (categorized as venovenous, venoarterial, and other). Complications (mechanical and patient) while receiving ECLS were recorded and made available for the asthmatic patients. Pre-ECLS disease-specific interventions were not recorded in the registry.

We performed a sensitivity analysis wherein we limited our analysis to the most recent 10 years of the ELSO registry (1997–2006) as advances in technology and management have occurred over the duration of the ELSO registry that could impact the results of our analyses and because covariates were limited in cases reported to the registry before 1997.

Statistics

Descriptive data were summarized as means with standard deviations or percentages. The Student's t-test was used to compare continuous variables, or, if non-normally distributed, rank sum tests were used, and the χ^2 statistic was used to compare categorical variables. Multivariable logistic regression was used to adjust for potential confounding. On the basis of the previous studies of factors associated with ECLS mortality, and biologic plausibility, we considered age, gender, race, length of mechanical ventilation pre-ECLS, acidosis (pH), and PaO_2/FiO_2 ratio pre-ECLS, presence of cardiac arrest pre-ECLS, and mode of perfusion as potential confounders.[7,18–23] Given the small number of mortality events in the asthmatic group, adjustment for potential confounding was performed one covariate at a time.[24] Survival to hospital discharge was reported as an odds ratio (OR) with 95% confidence intervals (CI), comparing the etiology of interest (asthmatics) to the remainder of the ECLS respiratory failure cohort. A p value ≤ 0.05 was used to signify statistical significance. Statistical analyses were performed using Stata 9.0 software (Stata Datacorp, College Station, TX).

Results

A total of 2,127 adult ECLS cases were reported to the ELSO registry between January 1986 and September 2006. Of these, 1,257 were adult respiratory failure ECLS cases. Survival to hospital discharge was 51.4% for the entire adult respiratory failure ECLS cohort.

Of these 1,257 cases, asthma was the primary indication in 24 patients and nonasthmatic cases accounted for the remaining 1,233 cases. None of the 24 asthmatic cases in the ELSO registry corresponded to the previously noted case reports. The most common etiologies of respiratory failure, and their respective survival to hospital discharge, are presented in **Table 1**. The 316 patients who did not have one of these etiologies were classified as "other."

Asthmatics, compared with nonasthmatics, were younger, received less mechanical ventilation pre-ECLS, maintained on ECLS for a shorter duration, more acidotic, and less hypoxic with higher PaO_2/FiO_2 ratios (**Table 2**). Venovenous ECLS was used more frequently in the asthmatic group, whereas venoarterial ECLS was used more frequently in nonasthmatics (**Table 3**). Details for the 24 asthmatics are provided in **Table 4**. Complications were noted in 19 of 24 asthmatic patients (**Table 5**). Each of the patients who did not experience a complication survived. Of the 24 asthmatics, 10 patients were reported to the registry before 1997 and 14 were reported between 1997 and 2006.

Table 1. Survival to Hospital Discharge for Adult Respiratory Failure Cohort Requiring Extracorporeal Life Support by Respiratory Failure Etiology, Listed by Diminishing Survival to Hospital Discharge

Etiology	No. Patients	Proportion of Cohort (%)	Survival to Hospital Discharge (%)
Asthma	24	1.9	83.4
Acute respiratory failure, NOS	70	5.6	64.3
Trauma	33	2.63	63.7
Viral pneumonia	100	8.0	63.0
Pneumonitis, aspiration	37	2.94	62.2
Sepsis	30	2.39	56.7
Bacterial pneumonia	225	17.9	52.0
ARDS	375	29.8	49.6
Pulmonary embolism	27	2.15	44.5
Other	316	25.1	43.4
Pulmonary hypertension	20	1.6	25.0
Total	1,257	100	51.4

ARDS, adult respiratory distress syndrome; NOS, not otherwise.

A total of 20 (83.3%, 95% CI 62.6%–95.3%) of 24 asthmatics survived to hospital discharge, compared with 626 (50.8%, 95% CI 47.9%–53.6%) of 1,233 nonasthmatic patients (OR favoring survival for asthmatics *vs.* nonasthmatics = 4.86, 95% CI 1.65–14.31, $p = 0.004$). Given the small number of mortal events in the asthmatic group, we present multivariable models adjusting one covariate at a time in **Table 6**. The relationship of asthma with improved survival remained significant after adjustment for each potentially confounding variable.

Table 2. Baseline Characteristics of Adult Respiratory Failure Cohort Requiring Extracorporeal Life Support (Continuous Variables Expressed as Mean ± SD)

	Asthmatic (n = 24)	Nonasthmatic (n = 1,233)	*p*
Age, yr	31.3 ± 12.3	38.3 ± 14.2	0.016
Male gender	67%	55%	0.34
Race, white*	72%	53%	0.10
Hours of mechanical ventilation pre-ECLS†	65.2 ± 67.7	109.5 ± 171.3	0.42
Hours on ECLS	111.9 ± 71.2	222.0 ± 228.1	0.003
Pre-ECLS cardiac arrest n, %	1 (4.17%)	80 (6.49%)	0.65
Pre-ECLS respiratory rate‡	17.4 ± 10.3	20.8 ± 9.5	0.20
Pre-ECLS PIP§	39.0 ± 8.88	40.9 ± 11.8	0.58
Pre-ECLS PEEP§	6.8 ± 3.3	13.0 ± 5.7	<0.001
Pre-ECLS pH*	7.17 ± 0.16	7.27 ± 0.13	0.003
Pre-ECLS $PaCO_2$*	119.7 ± 58.1	57.0 ± 23.8	<0.001
Pre-ECLS serum HCO_3*	35.9 ± 11.1	24.1 ± 7.48	<0.001
Pre-ECLS PaO_2/FiO_2 ratio*	244 ± 180	71 ± 68	<0.001

*Available in 15 asthmatics.
†Available in 14 asthmatics.
‡Available in 13 asthmatics.
§Available in 11 asthmatics.
SD, standard deviation; ECLS, extracorporeal life support.

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Table 3. Mode of Extracorporeal Life Support in Asthmatics and Nonasthmatics

Mode	Survival to Hospital Discharge by Mode (%)	Asthmatics	Nonasthmatics
Venovenous	58.9	14	551
Venoarterial	39.0	2	208
Venovenous to venoarterial conversion	20.6	0	34
Venoarterial to venovenous conversion	50	0	6
Other*	47.6	0	42
Total = 857 subjects with ECLS mode recorded	51.9	16	841

*Includes venovenous with a single double-lumen cannula or venoarterial with retrograde venous drainage.
ECLS, extracorporeal life support.

We conducted sensitivity analyses limited to the most recent 10 years of the ELSO registry, where there were 924 adult respiratory failure ECLS cases, and observed the same significant relationship between asthma and survival after adjustment for potential confounding. A total of 13 of 14 (92.8%) asthmatics survived to hospital discharge, compared with 506 of 998 (51.0%) nonasthmatic patients (age-adjusted OR favoring survival for asthmatics *vs.* nonasthmatics = 11.2, 95% CI 1.4–86.8, $p = 0.02$).

Discussion

A recent trial reported that ECLS improved survival compared with conventional management strategies in patients with potentially reversible acute respiratory failure.[4] The reversible nature of status asthmaticus could maximize the potential benefits of ECLS, but important questions regarding the safety and outcomes of ECLS use for status asthmaticus remain unanswered. To inform this debate, we identified and described the outcomes of 24 patients who received ECLS for refractory status asthmaticus using the multicenter ELSO registry. We found that status asthmaticus seems to be associated with greater survival than other indications for ECLS, even after adjusting for known factors associated with ECLS mortality. However, important questions remain that preclude recommending the use of ECLS as the preferred salvage treatment option for these patients at this time.

First, whether ECLS confers a survival advantage in refractory status asthmaticus, compared with other treatment options, remains unknown. Despite limited power to detect a significant difference, we found that the survival outcomes for status asthmaticus seem favorable when compared with other indications for ECLS use. Over the most recent decade, we found that 93% of patients receiving ECLS for status asthmaticus survived and these favorable outcomes persisted after adjusting for potential confounders. However, we cannot predict how these patients would have fared had they not received ECLS. Although it is estimated that 7%–8% of mechanically ventilated asthmatics will not survive their hospitalization,[7,8] a precise estimate of mortality for the most severe cases is not known. To answer this question adequately will require more precise estimates of mortality for near-fatal asthma cases in general and for cases in which ECLS is used.

Second, although specific criteria exist for initiating ECLS in some etiologies of respiratory failure such as adult respiratory distress syndrome,[25] criteria do not exist for the initiation of ECLS for refractory status asthmaticus. Furthermore, clinicians are unable to predict when bronchospasm will subside in severe asthma.[7] From this perspective, it would be reasonable to ask whether ECLS was unnecessary in some asthmatics, which could have resulted in a differential survival bias. In those patients in whom data were reported, it seemed that the asthmatics were experiencing severe hypercapnic acidosis that their physicians viewed as worsening at a point in time when most patients with status asthmaticus are being liberated from ventilatory assistance.[26,27] Therefore, at least some of the asthmatics seem to be at the extreme of the disease severity spectrum, which would serve to mitigate the potential survival bias favoring status asthmaticus. However, if that were entirely the case, we would expect that the peak inspiratory pressures in the asthmatics would be significantly more elevated than were reported to reflect the dynamic hyperinflation that would be present. If we assume dynamic hyperinflation had developed to a degree that impending cardiovascular collapse was possible, we then need to ask whether clinicians adhered to standard and advanced pharmacologic and mechanical ventilation strategies which prove successful in most status asthmaticus cases before instituting ECLS.[28] Unfortunately, the details of care provided to patients before instituting ECLS are not available within the ELSO registry. These concerns illustrate the need for thorough reporting to the ELSO and underscore the potential of the ELSO registry to serve as a mechanism to better understand rare use of ECLS such as its use for status asthmaticus.

An informed decision of whether to consider initiating ECLS in refractory status asthmaticus also requires a better understanding of the morbidity associated with its use. In the current study, we found that complications of ECLS seem to be common. Mechanical and bleeding complications were the most commonly observed complications, but serious cardiovascular (*e.g.*, cardiac arrest) and neurologic (*e.g.*, brain death) complications were also observed. The number of complications for the asthmatic group seemed to be comparable with previously published data for adult ECLS.[18,25] These findings suggest that asthmatics experienced complications in similar proportions to the broader ECLS patient population despite a shorter duration of ECLS use. Whether, and to what degree, the observed outcomes were attributable to the reported complications is unknown, and further investigation into this association is required.

As hypothesized, our findings suggest that ECLS use for status asthmaticus is associated with favorable survival relative to other ECLS indications. However, the ELSO registry is voluntary; as such, there exists potential for information bias. Although centers are encouraged to report all ECLS cases, irrespective of outcome, and the number of cases not reported

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Table 4. Characteristics of the 24 Asthmatics Receiving ECLS by Yr of Age

Pt	Age	Yr	Gender	Race[†]	Hours of MV pre-ECLS	Pre-ECLS pH	Pre-ECLS $PaCO_2$	Pre-ECLS PaO_2/FiO_2 Ratio	Mode of ECLS[‡]	Hours on ECLS	Survival
1	19	2004	Male	B	87	7.18	130	647	VV	40	Yes
2	19	2001	Female	B	7	7.00	119	173	VV	171	Yes
3	20	1998	Male	B	37	7.00	138	492	VV	188	Yes
4	20	2004	Male	B	16	7.01	164	481	VV	23	Yes
5	20	1995	*	*	*	*		*	*	211	No
6	21	1996	Male	H	*	7.31	77	62	VV	382	No
7	23	2004	Female	W	117	7.43	49	245	VV	68	Yes
8	25	1999	Male	W	7	7.00	134.3	285	VV	23	Yes
9	25	2004	Female	B	229	6.99	248	75	VV	23	No
10	25	1994	*	*	*	*		*	VA	104	Yes
11	26	1996	*	*	*	*		*	*	71	Yes
12	28	1999	Female	W	42	7.27	90	71	VV	119	Yes
13	28	1993	*	*	*	*		*	*	108	Yes
14	28	1996	*	*	*	*		*	*	158	Yes
15	30	2000	Female	W	7	7.06	211	356	VV	75	Yes
16	33	1992	*	*	*	*		*	*	27	Yes
17	33	1994	*	*	*	*		*	*	117	Yes
18	35	1999	Male	W	75	7.24	92.3	221	VV	128	Yes
19	37	1998	Male	W	29	7.1	153	145	VV	99	Yes
20	37	1994	*	*	*	*		*	*	79	Yes
21	44	1996	*	*	*	*		*	*	11	No
22	57	2000	Male	W	163	7.39	63	68	VV	356	Yes
23	58	2002	Male	W	94	7.19	82.5	229	VV	64	Yes
24	60	2002	Male	A	3	7.35	44.3	106	VA	41	Yes

*Not available.
[†]Race categorized as white (W), black (B), Hispanic (H), Asian (A), and other.
[‡]Mode categorized as venovenous (VV) or venoarterial (VA).
ECLS, extracorporeal life support; MV, mechanical ventilation.

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Table 5. Complications Observed in the 24 Asthmatics Receiving ECLS

Complication	No. Patients	Proportion (%)
Bleeding (cannula or surgical site bleeding)	6	25.0
Bleeding (pulmonary hemorrhage)	3	12.5
Cardiovascular (use of vasoactive agents or arrhythmia)	6	25.0
Cardiovascular (cardiac arrest)	2	8.3
Infection (culture proven)	2	8.3
Mechanical (oxygenator failure, cannula problems, clot formation, and air in the circuit)	10	41.6
Neurologic (brain death or CNS hemorrhage)	3	12.5
Renal failure (requiring dialysis or hemofiltration)	3	12.5

ECLS, extracorporeal life support; CNS, central nervous system.

is presumed to be low,[18] it is possible that a reporting bias exists that could undermine our mortality estimates and our comparison between asthmatic and nonasthmatic ECLS cases. Unfortunately, a randomized controlled trial to assess the efficacy of ECLS in refractory status asthmaticus seems to be an unrealistic goal given the apparent rare use of ECLS for this disease. For these reasons, it is imperative that clinicians report all ECLS cases, including interventions received and indication for initiation, and outcomes to the ELSO registry to further our understanding of this potentially life-saving intervention.

A second potential limitation is uncontrolled confounding as several covariates were not measured (severity of illness) or were not available (site of ECLS use). Furthermore, we were unable to assess what role, if any, cardiovascular instability played in the decision to initiate ECLS and the outcomes observed. Although the rare use of venoarterial ECLS in asthmatics, compared with its more frequent use in nonasthmatics, suggests that hemodynamic stability differed across groups, the effect of asthma on mortality persisted after adjusting for mode of ECLS. Nevertheless, hemodynamic stability could explain a portion of the apparent survival advantage of status asthmaticus (and viral pneumonia) and survival disadvantage of pulmonary hypertension and future studies should explore this potential association. In addition, we acknowledge that nonasthmatics were likely more ill by conventional measurements (*i.e.*, APACHE, SOFA) and this uncontrolled confounding could explain some of the observed outcome differences. However, this is why we hypothesized that a disease process such as status asthmaticus, which may be limited to a single organ, would maximize the benefit of ECLS by being acute and severe, yet reversible.

Table 6. Odds Ratios of Survival to Hospital Discharge for Asthmatics *vs.* Nonasthmatics, Adjusted for Each Potential Covariate, One Covariate at a Time

Logistic Regression Model	Total N in Model	Odds Ratio (95% CI)	*p*
Base model without adjustment	1,257	4.86 (1.65–14.31)	0.004
Adjusted for			
Age	1,257	4.28 (1.44–12.67)	0.009
Pre-ECLS cardiac arrest	1,257	4.82 (1.64–14.19)	0.004
Mode of ECLS	856	5.71 (1.28–25.52)	0.023
Race	842	7.01 (1.54–31.89)	0.012
Gender	839	5.97 (1.34–26.66)	0.019
Hours of MV pre-ECLS	814	11.50 (1.50–88.32)	0.019
Pre-ECLS pH	799	8.36 (1.84–38.0)	0.006
Pre-ECLS PaO_2/FiO_2 ratio	769	5.60 (1.21–25.99)	0.028

ECLS, extracorporeal life support.

In conclusion, our study revealed that ECLS is being used, albeit rarely, in refractory status asthmaticus. Status asthmaticus, as an indication for ECLS use in adult respiratory failure, seemed to be associated with greater survival than other indications for ECLS. Despite the potential benefits of ECLS, complications seemed to be common and whether ECLS confers a survival advantage compared with other salvage treatment options remains unknown. Further investigations are required to determine whether and when the potentially life-saving intervention of ECLS should be initiated in the asthmatic failing conventional therapy.

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