Complications of neonatal extracorporeal membrane oxygenation

Collective experience from the Extracorporeal Life Support Organization

Since 1973, 7667 neonates have been treated with extracorporeal membrane oxygenation for severe respiratory failure and their cases reported to the Extracorporeal Life Support Organization Registry. The overall survival was 81 % in these neonates, who were thought to have a survival of 20 % without extracorporeal membrane oxygenation. A total of 4322 mechanical complications (0.56 ± 0.84 per case) and 13,827 patient complications (1.80 ± 2.12 per case) were reported overall. The most common mechanical complications included clots in the circuit (19 %), cannula placement (9 %), oxygenator failure (4 %), and others (9 %). Common patient complications included cardiopulmonary (43 %), neurologic (35 %), bleeding (35 %), metabolic (32 %), renal (25 %), and infectious (9 %). From the initial experience to 1988 the average number of mechanical complications per case was 0.27 per case and this significantly increased during 1990 to 1992 to 0.75 per case ($p < 0.05$). Likewise, from 1973-1985 to 1988 the average patient complications per case were 1.44 per case and this significantly increased during 1990 to 1992 to 2.10 per case. During the same periods, patient survival significantly decreased from 84 % (1973-1985 to 1988, $n = 2463$) to 80 % (1990 to 1992, $n = 4005$). Venovenous double-lumen single cannula extracorporeal membrane oxygenation had a higher survival than venoarterial extracorporeal membrane oxygenation (91 % versus 81 %) and a lower rate of major neurologic complications. The incidence and survival with seizures (6 % and 89 % venovenous versus 13 % and 61 % venoarterial) or cerebral infarction (9 % and 69 % venovenous versus 14 % and 46 % venoarterial) was significantly lower with the venovenous method and appeared to have a substantial impact on overall survival. The correlation of patient complication rate and total complication rate with survival was highly significant, however, causality cannot be established. Explanations for the increase in complications, relative to a decrease in survival, despite a growing nationwide experience include (1) increased complexity of cases as many programs expand entry criteria (more premature infants, infants with grade 1 or 2 intracranial hemorrhage, and complex congenital diaphragmatic hernia), (2) a growing number of programs with fewer cases per program, yet greater accessibility, (3) less reluctance to report complications encountered during extracorporeal membrane oxygenation as group experience grows, and (4) changes in the Extracorporeal Life Support Organization data form to be more inclusive of more minor complications. (J THORAC CARDIOVASC SURG 1994;107:838-49)

Joseph B. Zwischenberger, MD, Thuan T. Nguyen, MD, J. Robert Upp, Jr., MD,
Phillip E. Bush, BS, Charles S. Cox, Jr., MD, Tom Delosh, BS, and Lyle Broemling, PhD,
for the Extracorporeal Life Support Organization (ELSO)

From the Extracorporeal Life Support Organization.

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Address for reprints: J. B. Zwischenberger, MD, Division of Cardiothoracic Surgery, University of Texas Medical Branch, Galveston, TX 77555-0528.

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Extracorporeal circulation for respiratory failure was first attempted in newborn infants by Rashkind and associates.¹ After a series of laboratory studies, Bartlett and coworkers² began clinical trials of extracorporeal membrane oxygenation (ECMO) in 1972 and reported the first successful use of ECMO in neonatal respiratory failure in 1976. Subsequently, two prospective randomized

**Table I. Criteria and outcome for neonatal ECMO
(n = 7667)**

	Percent of total	Survival (%)
Oxygenation index	28	85
Failure to respond to maximum therapy	26	80
Acute deterioration	21	76
Alveolar-arterial oxygen gradient	17	87
Barotrauma	2	86

studies helped establish ECMO as the treatment of choice for term newborn infants with severe respiratory failure.^{3,4} Although ECMO has been used since 1975, systematic collection of data was not begun until 1985. As of January 1993, ECMO has been used in the treatment of more than 7667 neonates in 99 centers worldwide (17 outside North America) with an overall survival of 81%⁵ in neonates thought to have a survival rate of 20%. The purpose of this study was to review the registry data on complications of neonatal ECMO and to examine trends in the number of complications and the impact on survival.

Materials and methods

Data for this report were obtained from the Neonatal ECMO Registry (hereafter referred to as the Registry) of the Extracorporeal Life Support Organization (ELSO), after written permission was obtained from the ELSO Steering Committee. ELSO is a consortium of physicians, scientists, and health care personnel interested in the study and practice of extracorporeal life support. Participation in the Registry is voluntary but universal among member centers.

Data forms for the Registry were originally conceived and circulated among known active centers (18 centers) in 1985. The data on patients treated before that time were retrospectively obtained by chart review at each center. These data were considered a single entry (1973-1985) for this report. From 1985 to date, data forms were voluntarily completed at the time of patient discharge from the hospital or death. Since 1985 the data form has undergone four separate revisions to better detail the course and circumstances of the patient treated with ECMO. All data forms are approved and signed by the participating program director or designee responsible for accuracy of the data before data entry. Data were entered on a personal computer running the FoxPro database program and analyzed with Microsoft Excel software (Microsoft Corp., Redmond, Wash.). Individual patient data forms were not reviewed as part of this study, thereby maintaining confidentiality.

Statistics are expressed as mean $\pm$ standard deviation. Discrete variables were compared with the χ^2 test and significance was declared when $p < 0.05$. Linear regression analysis was used to measure the association between the annual patient and mechanical complication rates and the annual patient survival rate. Statistical computations were done with the Number Cruncher Statistic System, version 5.0 (NLSS, Kaysville, Utah), on a personal computer.

Fig. 1. Total number of active ECMO centers per year and average number of cases per center per year.

Although there are some differences in patient management, most centers practiced similar techniques of venoarterial (VA) ECMO as described and modified by Bartlett and associates.^{2,6,7} Since 1990, single-cannula, double-lumen venovenous (VV DL) ECMO has been available and has increased in application.^{8,9} Total support of gas exchange with venovenous perfusion returning perfusate blood into the venous circulation has the advantage of avoiding carotid artery ligation in the neonate.

Results

From 1973 to January 1993, 7667 newborn infants were treated with ECMO at 99 centers (17 centers outside North America) and data reflecting their clinical course were voluntarily submitted to the Registry. Fig. 1 shows the number of ECMO centers opening each year and cumulative active centers, as well as the average number of cases per center per year. The survival rate for the entire series, including all of the early cases, was 81% (Fig. 2). The criteria for use of ECMO recognized by the Registry and their prevalence in this report were as follows: oxygenation index 28%, failure to respond to maximum treatment 26%, acute deterioration 21%, alveolar-arterial oxygen gradient 17%, and barotrauma 2%. Other criteria have been used but are now obsolete or represent less than 1% (see Table I). The average duration of ECMO was 141 ± 89 hours. Outcome by primary respiratory diagnosis (Table II) in decreasing percentage of survivors who received ECMO included meconium aspiration 94%; primary pulmonary hypertension/persistent fetal circulation 84%; hyaline membrane disease/respiratory distress syndrome 83%; β -streptococcal pneumonia/sepsis 77%; and congenital diaphragmatic hernia 59%. Table I documents survival as a function of selection criteria. Oxygenation index (85%) and alveolar-arterial oxygen gradient (87%) yielded a similar survival. Patients who received ECMO because of acute deterioration had a 76% survival, which reflects the emergency initiation of ECMO in this group. As previously noted by Stolar, Snedecor, and Bartlett,¹⁰ failure of maximal therapy

Fig. 2. Annual patient survival rate and annual total patients treated with ECMO.

Table II. Aggregate survival by diagnosis (n = 7667)

	Survival (%)	Frequency (%)	ECMO duration (hr)	Complications/case	
				Mechanical	Patient
Meconium aspiration syndrome	94	38	123.9 ± 64.2	0.46	1.38
PPHN/PFC	84	12	127.7 ± 86.7	0.50	1.56
HMD/RDS	83	12	127.0 ± 72.0	0.52	1.66
Pneumonia/sepsis	77	15	132.8 ± 85.0	0.57	2.32
CDH	59	19	189.2 ± 117.8	0.82	2.44

PPHN/PFC, Primary pulmonary hypertension/persistent fetal circulation; HMD/RDS, hyaline membrane disease/respiratory distress syndrome; CDH, congenital diaphragmatic hernia.

Table III. Neonatal ECMO complications: mechanical (n = 7667)

Complication	n	Prevalence (%)	Survival (%)
Clots	1438	19	76
Cannula placement	718	9	77
Air in circuit	406	5	74
Oxygenator failure	339	4	64
Cracks in connectors	214	3	72
Pump malfunction	133	2	81
Heat exchanger malfunction	96	1	73
Raceway rupture	23	<1	61
Other	683	9	76

(clinical judgment) as an entry criterion might be criticized for lack of rigorous definition; however, this group (26% of patients) had only an 80% survival, which suggests the patients were either more desperately ill or ECMO entry was accomplished more, not less, stringently than in the other entry criteria groups.

There were 4322 mechanical complications reported in 7667 ECMO cases, or an average of 0.56 ± 0.84 mechanical complications per case. Mechanical complications, in descending order of frequency, as reported in

the Registry, included clots in the circuit, cannula placement, air in the circuit, oxygenation failure, cracks in pigtailed/connectors, pump malfunction, heat exchanger malfunction, raceway rupture, and mechanical "other" (see Table III). From 1973-1985 to 1988 the average mechanical complications per case was 0.27 per case and this significantly increased during 1990 to 1992 to 0.75 per case ($p < 0.05$; Fig. 3). Survivors had 0.52 ± 0.79 complications per case reported whereas nonsurvivors had 0.77 ± 1.02 complications per case reported ($p < 0.01$).

There were 13,827 patient complications in 7667 cases, or an average of 1.80 ± 2.12 complications per case. Of the registered ECMO patients, 32% had no medical complications. There was a 94% survival in patients with no medical complications. Survival decreased to 75% with one or more medical complications ($p < 0.01$). Survivors had 1.41 ± 1.68 complications reported per case whereas nonsurvivors had 3.53 ± 2.84 complications reported per case ($p < 0.01$). Neurologic complications (Table IV) were the most common major complication (35% of cases). Seizures and cerebral infarction documented by either cranial ultrasound or computed axial tomography were the most frequent neurologic complication. Cardiopulmonary complications accounted for 43% of med-

Table IV. Neonatal ECMO complications: patient (n = 7667)

Complication	n	Prevalence (%)	Survival (%)
Neurologic			
Seizures	1037	14	66
Infarction by HUS	1002	13	49
Infarction by CAT	264	3	84
Brain death	100	1	0
Other	317	4	73
Hemorrhagic			
Hemolysis	705	9	71
Cannula site	523	7	73
Surgical site	478	6	54
Gastrointestinal	205	3	54
Other hemorrhagic	571	7	66
Cardiopulmonary			
Hypertension	816	11	76
Myocardial stun	445	6	64
Pneumothorax	420	5	66
Arrhythmia	297	4	61
Symptomatic PDA	249	3	74
Pulmonary hemorrhage	212	3	50
CPR required	184	2	50
Other cardiopulmonary	551	7	65
Other pulmonary	341	4	64
Renal			
Dialysis/hemofiltration	994	13	60
Creatinine level >1.5 mg/dl	794	10	59
Other renal	162	2	60
Metabolic			
K ⁺ >6.0 mEq/L	224	3	49
K ⁺ <2.5 mEq/L	272	4	79
Na ⁺ >150 mEq/L	221	3	57
Na ⁺ <125 mEq/L	64	1	52
Ca ⁺⁺ >12 mg/dl	78	1	55
Ca ⁺⁺ <6 mg/dl	133	2	63
CHO >240 mg/dl	171	2	53
CHO <40 mg/dl	151	2	64
pH >7.6	372	5	80
pH <7.2	157	2	41
Other metabolic	143	2	69

HUS, Hemolytic uremic syndrome; CAT, computed axial tomography; PDA, patent ductus arteriosus; CPR, cardiopulmonary resuscitation; CHO, carbohydrate.

ical complications, hemorrhagic 35%, renal 25%, metabolic 32%, and infection 9% of total cases.

From 1973-1985 to 1988 the average number of patient complications per case was 1.44 per case and this significantly increased during 1990 to 1992 to 2.10 per case (Fig. 3). During the same periods patient survival significantly decreased from 84% (1973-1985 to 1988, $n = 2463$) to 80% (1990 to 1992, $n = 4005$; Fig. 4). The association between total complication rates and survival rate was examined by regression analysis (Table V). The correlation of patient complication rate and total complication rate with survival was highly significant; however, causality cannot be established.

Fig. 3. Average number of patient and mechanical complications reported per ECMO case by year. *All cases registered from 1973 through 1985 are considered as a single entry.

Fig. 4. Percent overall survival versus total complications (patient plus mechanical) per ECMO case by year. *All cases registered from 1973 through 1985 are considered as a single entry.

Table V. Association between patient, mechanical, and total complication rate with survival by regression analysis

Source	Equation	R ²	p Value
Patient	Survival = 94.92 - 7.41 · CR	0.98	0.00001
Mechanical	Survival = 85.71 - 6.84 · CR	0.43	0.07
Total	Survival = 92.21 - 4.55 · CR	0.88	0.0005

CR, Complication rate.

When the techniques of VA versus VVDL were compared the survival for VA (1990 to 1992, $n = 3146$) was 81% whereas that for VVDL (1990 to 1992, $n = 576$) was 91%. The average duration of VA ECMO was 141 ± 89 hours and of VVDL was 120 ± 64 hours. Conversion from VVDL to VA ECMO was reported in 101 patients with a 79% survival. The average number of mechanical complications per case during the same period was 0.69 for VA and 0.79 for VVDL. The average number of

patient complications per case was 2.06 for VA and 1.65 for VVDL. Comparison of specific mechanical complications demonstrated VVDL had a significantly higher prevalence of restrictive sutures (2% VVDL versus 0% VA) and kinking in the cannulas (9% VVDL versus 1% VA). The numbers of other mechanical complications were similar for both VA and VVDL. In comparison of specific patient complications between techniques, VVDL had a much lower rate of major neurologic complications. The prevalence and survival with seizures (6% and 89% VVDL versus 13% and 61% VA) or cerebral infarction (9% and 69% VVDL versus 14% and 46% VA) were significantly lower with VVDL and appeared to have a substantial impact on overall survival.

When different entry criteria (Table II) were compared for prevalence of mechanical and patient complications, no significant differences were apparent. This was not surprising inasmuch as each of the entry criteria was designed to identify the same patient population. When premature neonates (<35 weeks' gestation) were treated with ECMO, 36% of them had intracranial hemorrhage (ICH) with 62% mortality, whereas only 12% of neonates of more than 35 weeks' gestation had ICH with a 49% mortality. Similar findings were noted with low-birth-weight neonates (<2.2 kg): 28% had ICH with 64% mortality, whereas only 12% of neonates who weighed more than 2.2 kg had ICH with a 50% mortality.

Discussion

The treatment of the patient who receives ECMO, including mechanical and patient-related complications, spans the entire field of critical care.^{6, 7, 11-13} To understand the nature and relative frequency of the reported complications, one must review the patient selection criteria and basic ECMO techniques and management techniques used during the 10- to 15-year period of the expanding cumulative experience. The general indication for ECMO is acute, severe, reversible respiratory failure unresponsive to optimal ventilator and pharmacologic management but from which recovery can be anticipated within a reasonable period (10 to 14 days) of extracorporeal support. The requirement for systemic heparinization (30 to 60 U/kg per hour to maintain activated clotting times two to three times normal) limits the population for whom ECMO is appropriate; patients without life-threatening bleeding or without excessive risk for ICH. Criteria for instituting ECMO have also evolved during the 12 years of clinical experience contained in the Registry. The goal was to identify infants with a greater than 80% likelihood of dying. Included were neonates who, despite "optimum" medical management as defined by the caregiver, demonstrated acute deterioration, failure to respond to maximum treatment, uncontrolled tension

pneumothoraces or pneumomediastinum, or deterioration after diaphragmatic hernia repair.^{3, 14} Contraindications to ECMO included evidence of ICH (grade 1 or 2 is controversial) or other brain damage, multiple congenital anomalies, and irreversible lung damage.

In the original format as the Neonatal ECMO Registry, information was collected concerning patient demographics, pre-ECMO clinical features, ECMO indications, medical and technical complications, and short-term outcome. Between 1980 and 1987, 715 patients were registered as the collective retrospective experience from all participating ECMO centers.¹⁴ Technical complications were reported in 23% and patient-related complications in 65%. The survival for the first 10 patients at any one center was significantly worse than that for the subsequent 10 patients (75% versus 84%, $p < 0.01$), reflecting a learning curve. In 1991 Stolar, Snedecor, and Bartlett¹⁰ reviewed the demographics, clinical features, and short-term outcome in the Neonatal ECMO Registry of the ELSO (incorporated 1989, Ann Arbor, Mich.). Of 3528 infants with a greater than 80% predicted mortality rate, 83% survived when treated with ECMO. Both technical complications, reported in 25% of patients, and patient-related complications, reported in 75%, adversely affected survival. Normal function and development (up to 90%) at follow-up of ECMO survivors was encouraging and suggested that ECMO support can be accomplished safely and that subsequent normal development is frequent. Because of regional differences in patient populations, medical treatment protocols, and ventilator management, entry criteria are evaluated at each hospital before an ECMO program is initiated.¹⁵

Availability of ECMO and improved neonatal transport¹⁶ allowed a rapid growth of ECMO programs and application (cases per year) from 1985 to 1990 (Figs. 1 and 2). From 1990 to 1992 the growth curve leveled at approximately 1300 cases per year and new ECMO programs continued to develop. As shown in Fig. 1 this has resulted in a growing number of ECMO programs (99 total) with fewer cases per program (18.2 in 1988 to 13.2 in 1992). The price of more programs, thus greater accessibility and ECMO availability, has been a decreased overall experience per ECMO center with more critically ill neonates presenting for treatment. Coincident with the leveling of the number of cases per year has been the increased complexity of cases as many programs expand their entry criteria. In 1987, the overall survival of neonates treated with ECMO was 87% (Fig. 2). Many programs noted the strict criteria in use at that time and believed a substantial number of neonates outside the criteria would benefit from ECMO. Therefore some centers treated more premature infants, infants with grade 1 or 2 ICH, and complex congenital diaphragmat-

ic hernia. By 1992 the overall survival had decreased to 79.1% of neonates treated with ECMO.

As the Registry data became available (1986) there was a growing awareness of the frequency of complications and therefore less reluctance (or embarrassment) by individual centers to report their complications. As noted, the Registry data form was modified on four separate occasions to capture the prevalence of complications in more detail. Some confusion in reporting complications undoubtedly occurred. Unfortunately, the transition periods from one data form to the next were also not clear. Often centers would use old versions of the data form because of familiarity or according to local needs for yearly data collection or quality assurance. Also a lag time of several months would often occur between patient discharge, form completion, form approval, mail-in to the Registry, and data entry into the Registry. These parallel events contributed to the growing number of patient and mechanical complications reported per case by year from 1987 to 1992 (Fig. 3), as well as the increased number of total complications per case while survival significantly decreased (Fig. 4). Explanations for the increase in complications, relative to a decrease in survival, despite a growing nationwide experience include increased complexity of cases as many programs expanded entry criteria; a growing number of programs with fewer cases per program, yet greater accessibility; less reluctance to report complications encountered during ECMO as group experience grew; and changes in the ELSO data form to be more inclusive of more minor complications.

Mechanical complications are related to each major component of the circuit (Table III). One of the most common (9%) mechanical complications listed in the Registry was "other." This reflects the fact that, in addition to the identifiable components listed in the previous section, the entire circuit is subject to failure, including the bladder box, connectors, electrical components, power sources, plugs, oxygen sources, carbogen tanks, blenders, and circuit monitoring equipment. Clots in the circuit were the most common mechanical complication (19%). The assessment of a "significant" clot, however, is subjective. The extracorporeal circuit presents a large foreign surface for activation of neutrophils, lymphocytes, and platelets releasing inflammatory mediators and free-radical activity.^{17,18} Recently heparin-coated ECMO systems (Carmeda; Medtronic Cardiopulmonary, Anaheim, Calif.) have been developed for ECMO and may prove helpful to decrease bleeding during major operations with the use of ECMO.¹⁹

Cannulas are inserted with great care to avoid vascular damage during insertion, because loss of control of the internal jugular vein can result in massive mediastinal bleeding and dissection of the carotid artery intima can

progress to a lethal aortic dissection. The venous cannula, however, can be advanced too little or too much, either of which can cause cannula obstruction. Likewise, the venous catheter can enter the subclavian vein or cross the foramen ovalis. Anatomic variations of the right atrium (aneurysmal atrial septum or redundant eustachian valve) can also interfere with venous return. Insertion of the arterial cannula too far into the ascending aorta can cause increased afterload to left ventricular outflow and may contribute to left ventricular failure. In addition, the cannula can cross the aortic valve, causing aortic insufficiency. Insertion too far down the descending aorta can compromise coronary and cerebral oxygenated blood flow and cause "streaming" of hyperoxygenated blood from the ECMO circuit without adequate mixing. The distance from the orifice of the innominate artery to the takeoff of the right subclavian artery can be a remarkably short 1.0 to 1.5 cm. If the arterial cannula is pulled out to the point at which the arterial infusion selectively enters the right subclavian artery, the right upper extremity can be infused with the entire postoxygenator blood flow while the rest of the body remains hypoxic and cyanotic.

Air in the circuit (5% of mechanical complications) can represent a few small bubbles seen in the bladder to a complete venous air lock. Venous air lock usually results from dislodgment of the venous cannula so that one or more of the sideholes is outside the vessel.²⁰ Massive air-lock necessitates discontinuation of ECMO support with either removal of the air or repriming of an entire ECMO circuit. For small amounts of air in the venous line, one can move the air to the venous reservoir by sequentially raising the venous line to aspirate the air out of the venous reservoir.

Oxygenator failure recorded in the Registry has decreased in frequency to 4%; however, the Registry does not record the method of determining oxygenator failure. Some centers report failure when decreased oxygen or carbon dioxide transfer occurs. Other centers monitor preoxygenator and postoxygenator pressure gradients, platelet count, plasma free hemoglobin, and fibrin split products to demonstrate when the oxygenator may be causing a consumptive coagulopathy. Any failing membrane should be changed immediately on recognition to prevent an air/blood leak.²⁰

Tubing rupture has become much less frequent with the introduction of S 65 HL raceway tubing (Norton Performance Plastics, Inc., Akron, Ohio).²¹ Previously, polyvinyl chloride tubing necessitated advancement of the raceway every 24 hours to prevent tube fatigue and rupture. Pump failure, likewise, has become more rare as direct and belt-driven pumps have been manufactured specifically with long-term extracorporeal support in mind. Although heat-exchanger malfunction occurs in

only 1% of cases, it may cause severe hypothermia or hemodilution in the infant. Defective heat exchangers have been responsible for aluminum particle emboli; however, redesign has eliminated this problem.²²

Patient complications grouped by organ system are listed in descending order of frequency in Table IV. Because of systemic anticoagulation, bleeding complications are common. Moderate bleeding (<10 ml/hr) is frequently seen at the neck cannulation site. Intracranial, gastrointestinal, intrathoracic, abdominal, and retroperitoneal bleeding have all been observed in neonates receiving ECMO. With increasing regularity, major surgical procedures, particularly diaphragmatic hernia repair, are done immediately before or during ECMO.²³

During ECMO, infants are exposed to a number of conditions that may increase the risk of ICH, including ligation of the right common carotid artery and internal jugular vein, systemic heparinization, thrombocytopenia, coagulopathies, and systolic hypertension.^{24, 25} Although systemic anticoagulation may not cause ICH, it may allow rapid progression of hemorrhage.^{13, 24, 25} Patients in whom VA ECMO is used commonly have ligation of the right common carotid artery and internal jugular vein. Potentially decreased cerebral blood flow and increased cerebral venous hypertension have been considered as a source of ICH.²⁴⁻²⁶ Several authors have reported an increased incidence of right-sided central nervous system lesions in patients previously treated with ECMO.^{27, 28} Others have shown no evidence of a higher incidence of right-sided central nervous system lesions.²⁹ Noninvasive vascular studies have demonstrated adequate cerebral blood flow occurs during ECMO,³⁰ as well as early after decannulation³¹ and in late follow-up.³² No consistently lateralized electroencephalogram abnormalities were observed during or after ECMO when electroencephalogram tracings were compared with tracings obtained before cannulation of the right common carotid artery.³³ These studies suggest that, in neonates, when the common carotid artery is ligated, collateral circulation is readily established. Because of continued concerns about long-term common carotid artery ligation, a few centers reconstruct the artery at decannulation.³⁴⁻³⁶ Carotid reconstruction, however, introduces the potential for carotid dissection, thrombosis, emboli, or late stenosis.

During ECMO, platelets are altered as platelet aggregates form in the extracorporeal circuit and are preferentially sequestered in the lung, liver, and spleen. Thrombocytopenia in the neonate is significant in that existing bleeding may be exacerbated or bleeding may occur spontaneously. Thrombocytopenia can occur up to 4 days after the termination of ECMO for the treatment of neonatal respiratory failure; therefore, platelet counts should

be measured frequently during this critical period.³⁷ Hemolysis is a complication often related to the ECMO membrane or circuit.³⁸ Clots in the circuit or membrane may promote a coagulopathy by activation of complement, white blood cells, platelets, or coagulation factors to cause erythrocytes to adhere and lyse on the fibrin strands.¹⁷ Recent experience with aminocaproic acid (Amicar) suggests ICH may be decreased in prevalence and severity when this drug is given during ECMO.

In a retrospective analysis of neonates undergoing ECMO therapy, birth weight and gestational age were the most significant correlates with ICH that occurred during ECMO.^{39, 40} Our current review of the Registry data corroborates these findings. Most programs have avoided use of ECMO in infants of less than 34 weeks' gestation because of the prevalence of ICH. Differentiation between preexisting deficits and those secondary to ECMO remains difficult; however, some infants at high risk for brain damage (low Apgar scores, perinatal cardiac arrest, prolonged or profound hypoxia, prolonged fetal distress) have normal mental function, so definitive predictors of outcome have yet to be determined.

Systolic hypertension is dangerous during ECMO. Sell and associates⁴¹ reported that systolic blood pressures greater than 90 mm Hg developed in 38 of 41 newborn infants treated with ECMO. In 44% detectable intracranial hemorrhage developed and in 27% clinically significant ICH developed. The development of a medical management protocol with hydralazine, nitroglycerin, and captopril decreased the prevalence of clinically significant ICH from 50% before protocol therapy to 9% after protocol therapy.

Some degree of cardiac depression is fairly common early in the course of ECMO, particularly with severely asphyxiated patients.⁴²⁻⁴⁴ Hypocalcemia is a frequent occurrence after initiation of ECMO and can contribute to hypotension during ECMO.⁴⁵ Coronary arterial and abdominal organ blood flow is predominantly derived from the left ventricle during ECMO.⁴⁶ Impaired filling of the coronary arteries and persistent subendocardial ischemia during the early high-flow phases of ECMO may precipitate cardiac depression. Underlying congenital heart disease can be masked by respiratory failure in 2% of cases requiring ECMO.⁴⁷ VA ECMO can provide univentricular or biventricular cardiac support, thus extending the application of ECMO to infants and children in whom refractory postoperative cardiogenic shock develops after repair of congenital heart defects.^{48, 49}

Pericardial tamponade and tension hemothorax and/or pneumothorax have the common pathophysiologic effect of increasing intrapericardial pressure and decreasing venous return.⁵⁰ The triad of increased alveolar car-

bon dioxide tension and decreased peripheral perfusion (as evidenced by decreased pulse pressure and decreased venous blood oxygen saturation) followed by decreased ECMO flow with progressive hemodynamic deterioration is associated with tension pneumothorax.⁵¹ Sepsis is both an indication for and a complication of ECMO. However, positive blood cultures develop in only 5% of all patients requiring ECMO (Table IV). This is a remarkably low prevalence given the duration of cannulation, the large surface area involved, and the frequency of access to the circuit. Oliguria during ECMO is common, especially during the first 24 to 48 hours. Sell and associates⁵² reported the use of continuous hemofiltration for renal failure during ECMO.

Diagnosis-specific outcome analysis suggests more about the particular diagnosis than ECMO itself.¹⁰ Specifically, congenital diaphragmatic hernia necessitated ECMO for a longer duration (Table II), had more mechanical and patient complications per case, had significantly more hemorrhagic complications, and had subsequently poorer survival than other diagnoses. Of all the ECMO entry diagnoses, congenital diaphragmatic hernia is the only situation in which the patient has less than two completely developed lungs and requires an operation.²³ In congenital diaphragmatic hernia one cannot distinguish between persistent fetal circulation and pulmonary hypoplasia; therefore many centers treat all patients with diaphragmatic hernia who otherwise meet local ECMO criteria. Some centers require an arterial oxygen tension greater than 70 torr, others an arterial carbon dioxide tension less than 80 torr, at some time in the neonate's life as evidence of pulmonary parenchyma capable of gas exchange to avoid using ECMO to treat infants with fatal pulmonary hypoplasia. The hemorrhagic complications can be attributed to the major operation necessary to repair the diaphragmatic hernia, often immediately before or during ECMO.^{23, 53-55} The poorer survival can be related, in part, to the hemorrhagic complications, but also to pulmonary hypoplasia to a degree that may be incompatible with life.⁵⁶⁻⁵⁸ With the increased availability of ECMO, more infants with congenital diaphragmatic hernia, particularly the most desperately ill, will receive ECMO. Sepsis may be accompanied by multiple organ failure, which contributes to increased morbidity.

VVDL ECMO had a higher survival rate and a much lower rate of major neurologic complications. Although cases in which this technique was used may have been more carefully selected and "more stable" than VA ECMO cases, the early success of the technique is very encouraging.⁹ The less invasive VVDL technique may lead to an important conceptual change in the use of

ECMO technology. The current practice of waiting until the natural lungs become severely dysfunctional and then having to support cardiopulmonary function almost completely, as with VA ECMO, may give way to the concept of early lung assist.⁵⁹

Selection criteria remain problematic for a variety of reasons. They cannot be viewed as absolute because of variability between centers. What represents likely 80% mortality in one center may not apply to another. Historical controls are misleading because changing respiratory therapy strategies make historical populations difficult to compare. Also, once an ECMO center becomes established, a more challenging group of patients will be attracted than previously was the case. Further, a single entry criterion cannot be generalized for all entry diagnoses. Criteria for an 80% predicted mortality are probably not the same for meconium aspiration, congenital diaphragmatic hernia, primary pulmonary hypertension, and sepsis. Subsequent reports of patients registered in the Neonatal ECMO Registry of the ELSO will address these issues more thoroughly, as specific details of the pre-ECMO condition and therapeutic strategies are collected.

In conclusion, since 1973, 7667 neonates have been treated with ECMO for severe respiratory failure with an overall 81% survival in neonates thought to have a survival rate of 20% without ECMO. During ECMO, mechanical and patient-related complications are common. However, patient complication rate and total complication rate directly correlate with survival. VVDL ECMO has a higher survival rate and a significantly lower rate of major neurologic complications than VA ECMO. Congenital diaphragmatic hernia requires ECMO for a longer duration, has more mechanical and patient complications per case, has significantly more hemorrhagic complications, and has lower survival than other diagnoses. Prematurity (<35 weeks' gestation) increases the prevalence of ICH with increased mortality. This collective experience helps guide individual program quality assurance and identify trends that require reassessment of technique or patient management.

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Contributing ECMO centers

University of Michigan, Ann Arbor, Mich.
Children's Hospital, Pittsburgh, Pa.
Medical College of Virginia, Richmond, Va.
Oschner Clinic, New Orleans, La.
Columbia Presbyterian Hospital, New York, N.Y.
Children's Hospital of Michigan, Detroit, Mich.
Children's National Medical Center, Washington, D.C.
Cardinal Glennon Children's Hospital, St. Louis, Mo.
Georgetown University Hospital, Washington, D.C.
Kosair Children's Hospital, Louisville, Ky.
Miami Valley Hospital, Dayton, Ohio
Medical College of Georgia, Augusta, Ga.
Thomas Jefferson University Hospital, Philadelphia, Pa.
Children's Hospital Medical Center, Cincinnati, Ohio
Children's Hospital of Orange County, Orange, Calif.
Children's Hospital of Wisconsin, Milwaukee, Wis.
Children's Hospital of Boston, Boston, Mass.
Wilford Hall Medical Center, Lackland AFB, Tex.
Huntington Memorial Hospital, Pasadena, Calif.
St. Francis Medical Center, Peoria, Ill.
University of Texas Medical Branch, Galveston, Tex.
Carolinas Medical Center, Charlotte, N.C.
Primary Children's Medical Center (Inactive), Salt Lake City, Utah
Children's Hospital of Los Angeles, Los Angeles, Calif.
Emanuel Hospital and Health Center, Portland, Ore.

Children's Memorial Hospital, Chicago, Ill.
 Children's Mercy Hospital, Kansas City, Mo.
 University Medical Center—Texas Tech, Lubbock, Tex.
 Phoenix Children's Hospital, Phoenix, Ariz.
 St. Luke's Hospital, Boise, Idaho
 St. Joseph's Hospital & Medical Center, Phoenix, Ariz.
 St. Louis Children's Hospital, St. Louis, Mo.
 Minnesota Regional ECMO Program, Minneapolis, Minn.
 Cook County Hospital (Inactive), Chicago, Ill.
 Sutter Memorial Hospital, Sacramento, Calif.
 San Diego Regional ECMO Program, San Diego, Calif.
 UCLA Medical Center (Inactive), Los Angeles, Calif.
 Children's Hospital of Denver, Denver, Colo.
 LSPC Hospital at Stanford University, Palo Alto, Calif.
 James Whitcomb Riley Hospital, Indianapolis, Ind.
 Lutheran General Hospital, Park Ridge, Ill.
 Massachusetts General Hospital, Boston, Mass.
 Rainbow Babies and Children's Hospital, Cleveland, Ohio
 University of Nebraska Medical Center, Omaha, Neb.
 Children's Hospital of Alabama, Birmingham, Ala.
 Eastern Oklahoma Perinatal Center, Tulsa, Okla.
 Medical University of South Carolina, Charleston, S.C.
 Children's Hospital at Richland Memorial, Columbia, S.C.
 Miami Children's Hospital, Miami, Fla.
 Children's Hospital of Oakland, Oakland, Calif.
 Johns Hopkins Hospital, Baltimore, Md.
 Arkansas Children's Hospital, Little Rock, Ark.
 Alabama Neonatology Assoc.—St. Vincent's (Inactive), Birmingham, Ala.
 University of California at San Francisco, San Francisco, Calif.
 Presbyterian Hospital of Dallas, Dallas, Tex.
 Arnold Palmer Hospital for Women/Children, Orlando, Fla.
 Children's Hospital of Columbus, Columbus, Ohio
 Vanderbilt University Hospital, Nashville, Tenn.
 Children's Hospital and Medical Center, Seattle, Wash.
 LeBonheur Children's Medical Center, Memphis, Tenn.
 Children's Hospital of Philadelphia, Philadelphia, Pa.
 Duke University Medical Center, Durham, N.C.
 Children's Hospital of Dallas, Dallas, Tex.
 Shands Hospital at University of Florida, Gainesville, Fla.
 Sharp Memorial Hospital, San Diego, Calif.
 University of Chicago Medical Center, Chicago, Ill.
 Santa Rosa Medical Center, San Antonio, Tex.
 Long Beach Memorial Hospital, Long Beach, Calif.
 Christ Hospital and Medical Center, Oak Lawn, Ill.
 Eggleston Children's Hospital, Atlanta, Ga.
 Children's Hospital—Oklahoma, Oklahoma City, Okla.
 Newark Beth Israel Medical Center, Newark, N.J.
 Hershey Medical Center, Hershey, Pa.
 St. Christopher's Hospital, Philadelphia, Pa.
 University of Virginia Medical Center, Charlottesville, Va.
 University of New Mexico, Albuquerque, N.M.
 Butterworth Hospital, Grand Rapids, Mich.
 Children's Hospital of Buffalo, Buffalo, N.Y.
 Cook—Fort Worth Children's Medical Center, Fort Worth, Tex.
 Hermann Hospital, Houston, Tex.
 Yale University, New Haven, Conn.
 Texas Children's Hospital, Houston, Tex.
 Joe DiMaggio Children's Hospital at Memorial, Hollywood, Fla.

Rockford Memorial Children's Hospital, Rockford, Ill.
 Central Hospital, Kasugai, Japan
 Universitäts-Kinderklinik-Mannheim, Mannheim, Germany
 Robert-Debre Hospital, Paris, France
 Karolinska Institutet, Stockholm, Sweden
 Royal Alexandra Children's Pav., Edmonton, Canada
 Groby Road Hospital, Leicester, England
 Royal Children's Hospital, Parkville, Australia
 Prince of Wales Children's Hospital, Randwick, Australia
 Salesi Children's Hospital, Ancona, Italy
 St. Radoud Hospital, Nijmegen, The Netherlands
 National Children's Hospital, Tokyo, Japan
 Hospital for Sick Children, Toronto, Canada
 Montreal Children's Hospital, Montreal, Canada
 Free University of Berlin, Berlin, Germany
 Universitäts Kinderklinik Graz, Graz, Austria
 Sophia's Children's Hospital, Rotterdam, The Netherlands
 The Hospital for Sick Children, London, England
 Ospedali Riuniti, Bergamo, Italy
 Royal Hospital for Sick Children, Glasgow, Scotland
 Academisch Hospital Maastricht, Maastricht, The Netherlands

Discussion

Dr. Winfield J. Wells (*Los Angeles, Calif.*). We appreciate your bringing this huge experience to us. Your report contains a large amount of interesting information. This type of report is going to assume increasing importance inasmuch as it is really an outcome study. Outcome studies may have great importance as concerns what we are allowed to do in the future. For that reason, we need to analyze the data generated by these large multiinstitutional outcome studies carefully, and I believe there are some problems in the analysis of these data.

The first problem relates to complications. The authors make the point that the number of complications increases over the time span of the study. However, there may be reasons other than an increasing prevalence of complications. For instance, the data form changed four times during the period of the study. My first question, therefore, is this: Are the authors absolutely sure that more complications are occurring currently than did in the past, or could it be that more complications are being reported and the prevalence is unchanged?

Dr. Zwischenberger. I greatly appreciate the comments by Dr. Wells because he shares a broad experience in the use of ECMO. He is absolutely right. The problems with this study are as follows. First, with a greater than 7500-patient experience in 100 centers coming on-line over 15 years, it is difficult to pinpoint when experience was acquired or when individual physicians gained the experience necessary to try to avoid complications.

Second, as time has passed and the number of cases has leveled with the increasing number of centers, the experience per center has been diluted.

Third, as the ELSO database was accrued, it became apparent we were often talking about patient management problems, not necessarily about complications. In fact, we were learning from those problems all along. As we shared experiences among other centers we learned it is difficult to label these as problems or complications when there is a patient receiving extracorporeal support for 5, 10, or 15 days at a time.

Fourth, as Dr. Wells correctly identified, as ELSO tried to

capture more data they kept adding to the complication list, and to be good citizens of the Registry, program directors became more willing to report those complications.

As pointed out in the manuscript, it is impossible to determine the impact of these different variables and their impact on the data. We were careful to recognize trends from the data, not draw conclusions.

Dr. Wells. There is also the implication that the survival is decreasing, and several potential reasons are given. Would the authors be prepared, as we may be asked to do from such outcome studies in the future, to draw conclusions about which patients should or should not be offered ECMO? Further, would they be prepared to make a decision about which centers should or should not do ECMO on the basis of some minimal level of experience? This gets into the question of access versus outcome. Have we given up better results to make ECMO more accessible on a geographic basis?

Dr. Zwischenberger. That is an incredibly powerful and important question. I think it is absolutely imperative to answer that this database was not designed for nor can it be used to make those conclusions. This was a retrospectively derived and voluntarily submitted database from member institutions of ELSO. The fact that the survival rate has gone from 87% to 79% is a trend that is worth noting but it is not a disaster, especially when it is recognized that almost every center during that period of time was "testing the water." They were expanding their entry criteria from the very strict criteria first described by Bartlett in the early 1980s. As programs have embraced more difficult patients (more premature infants, those with more complex problems, and those with grade 1 or grade 2 intracranial hemorrhages), they have realized acceptable survival rates. I think a 79% survival is excellent in view of the patient population.

About the question of which centers should or should not be active, I think accessibility to health care is a major issue that the ELSO Registry is not prepared to address. Certainly having an ECMO center in a hospital means that infants within that hospital have much greater accessibility and would not have to endure a high-risk transport to another center. Thus accessibility in such cases could be very much to the advantage of the local center, yet there may be two other hospitals in the same city that have ECMO. I do not think the database is able to answer the broader social question of access versus outcome.

Dr. Wells. We thank you for bringing these data to us. My guess is that studies like this are going to be used to make conclusions about who should and should not be doing things. This is worrisome and we should all be careful in our analysis of these large, multicenter studies.

Dr. James B. D. Mark (Stanford, Calif.). I do not know anything about ECMO per se. I know it goes on at our center and at many others, but one wonders if we are not seeing a phenomenon such as we are seeing in coronary artery bypass operations or heart transplants. There are about half the number of ECMO centers as there are heart transplant centers, about 80 to 160. There are more centers, fewer cases per center, more complications, and lower survival. One might ask how one decides whether to open another center for ECMO. Is it purely a local decision, or is there some organizational decision-making?

Every hospital has its own air force these days and it is not that difficult to transport an infant some distance. Agreed, there is some risk, but if they are transported to a center where the risk is higher, it seems the gain has been offset. How does one decide when to open another ECMO center?

Dr. Zwischenberger. I agree with everything you just said, and the answer is that I do not know. Up until now, ECMO centers have been started on the basis of local enthusiasm and the ability of the center or the healthcare providers to identify a need at their center. As you well know, ECMO is a technique used in the treatment of critically ill patients and those patients can be neonates, as I described here, or they can be pediatric patients, or they can even be postcardiotomy patients. Each of these different populations has different physicians taking care of them and a different perceived need. I cannot say what captures the enthusiasm of the individual center.

Dr. Louis Brunsting (Ann Arbor, Mich.). My question relates to the difference in cerebral complications in the VVDL group versus the VA group. This study is a Registry study, but if the database includes patient characteristics for preoperative or pre-ECMO comorbidities, have you gone back and done a risk-adjusted case-controlled study between the VVDL and VA groups? If you have, could you share with us those results?

Dr. Zwischenberger. Your observation is correct. That study needs to be done, but I thought it was beyond the scope of this overview to do so. As you well know, the pre-ECMO course of the patients has only been captured in the later version of the ELSO Registry form, and I felt that was the subject of a separate study. But, you are right, the study has to be done because the implication is that we are all remiss for not doing VV ECMO exclusively. Anyone who has done single-cannula VV ECMO knows it is technically more difficult. The patient's condition must be hemodynamically stable because it provides no cardiac support and gas transfer is marginal, but it is an effective technique that needs to be further explored.

Dr. Michael Wood (Burlingame, Calif.). Do you have any data or outcome information regarding what happens to these children as they grow up? Your experience is quite large with more than 7500 children, and I do note that your experience was limited in the early years; however, I would be interested in finding out what, if any, outcome data have been generated.

On the other end of the age spectrum, we can be criticized for operating on 80-year-old patients, but given good outcome data, the health care providers are satisfied. We would be quite interested in learning more about your own outcome data including neurologic outcome, education potential, and overall patient satisfaction given that you are dealing with infants with, we hope, a long life expectancy.

Dr. Zwischenberger. The ELSO Registry in its current form does not obtain follow-up. There is a separate effort by the ELSO organization for follow-up that is currently being done. A review of the literature reveals about 80% to 85% of patients who survive ECMO treatment are considered normal by the measures that we have on young children. About 15% are abnormal, and of those 15%, about a third are mildly abnormal, a third are moderately abnormal, and a third are severely abnormal.