Reversal of Mortality for Congenital Diaphragmatic Hernia with ECMO

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Extracorporeal Membrane Oxygenation (ECMO) has been available to neonates with respiratory failure at the University of Michigan School of Medicine since June 1981. In order to evaluate the impact of this type of pulmonary support, a retrospective analysis of 50 neonates with posterolateral congenital diaphragmatic hernia (CDH) who were symptomatic during the first hour of life and were treated between June 1974 and December 1987 was carried out. The patients were divided into two groups, those treated before June 1981 (16 patients) and those treated after June 1981 (34 patients). Overall survival improved from 50% (eight of 16 patients) during the pre-ECMO era to 76% (26 of 34 patients) during the post-ECMO period ($p = 0.06$). During the period after June 1981, 21 neonates were unresponsive to conventional therapy and were therefore considered for ECMO. Failure of conventional therapy was defined as acute clinical deterioration with an expected mortality of > 80% based on an objective formula previously reported. Six patients were excluded on the basis of specific contraindications to ECMO. Thirteen of 15 infants (87%) supported with ECMO survived. Three patients treated before 1981 met criteria for ECMO; all three died while receiving treatment using conventional therapy. These survival differences are significant ($p < 0.01$). In addition, the survival of 87% for the infants treated with ECMO *versus* the expected mortality of > 80% for these same patients when treated with conventional therapy is highly significant ($p < 0.005$). Based on this data, ECMO appears to be a successful, reliable, and safe method of respiratory support for selected, critically ill infants with CDH.

DESPITE IMPRESSIVE ADVANCEMENTS in surgical and neonatal intensive care over the last two decades, the mortality of infants born with congenital diaphragmatic hernia (CDH) presenting for treatment within the first 24 hours of life has remained approximately 50% (Table 1).[1-9] Extracorporeal membrane oxygenation (ECMO) was introduced in 1975 as a treatment for acute respiratory failure in neonates unresponsive to conventional mechanical ventilation.[10] Since then, in the United States, over 1000 infants with diagnoses such as sepsis, meconium aspiration syndrome, and CDH have been cared for with ECMO, often with impressive improvements in survival.[11] Children with CDH remain problematic. Recent reports from established ECMO centers have shown survival rates of 35–58% in infants with CDH.[12,13] Our institutional survival rate for infants with CDH who were treated with ECMO exceeds 85%, and the corresponding overall survival rate for infants with CDH is 76%. This report presents our institutional experience, including selection criteria, methodology, and results for ECMO in the treatment of severe CDH presenting within the first hour of life.

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Materials and Methods

A retrospective review of all patients with CDH treated at the University of Michigan, Mott Children's Hospital, from June 1974 to December 1987, was performed.

ECMO therapy became available for the management of CDH patients with postoperative pulmonary failure in June 1981. This date was used to divide the series into two groups: Group 1 refers to patients treated before June 1981 in the "pre-ECMO era," and Group 2 designates those seen during the "ECMO era". Patients in Group 1 were further divided into "ECMO candidate" or "non-candidate" groups by retrospectively applying ECMO selection criteria to these patients. Those in Group 2 were divided into "ECMO-treated" and "conventional management" groups.

The technique of extracorporeal support of neonates with respiratory failure has been well-described else-

TABLE 1. *Historical Comparison of Survival in CDH Reports (1965–1985)*

Date	Authors	CDH Patients	Survival
1965	Snyder and Greaney[1]	23	11 (48%)
1967	Johnson and Koop[2]	34	18 (53%)
1965	Raphely and Downes[3]	17	8 (47%)
1973	Raphely and Downes[3]	32	9 (28%)
1980	Ein[4]	69	28 (41%)
1981	UMMC (not published)	16	8 (50%)
1982	Weiner[5]	66	28 (42%)
1983	Fonkalsrud[6]	15	8 (53%)
1984	Hansen[7]	75	40 (53%)
1984	Reynolds[8]	97	58 (60%)
1984	Bohn[9]	58	30 (52%)

UMMC = University of Michigan, Mott Children's Hospital.

where.[14] Since June 1981, patients with significant deterioration of pulmonary function despite the use of maximal conventional ventilatory and pharmacologic support were considered for ECMO. Specific exclusion and inclusion criteria for ECMO have been developed to standardize the evaluation process (Tables 2 and 3). A patient was excluded for consideration for ECMO if the patient had any of the following: 1) age greater than 7–10 days; 2) estimated gestational age (EGA) less than 35 weeks (due to the prohibitively high incidence of intracranial hemorrhage in less mature neonates);[14] 3) pre-existing intracranial hemorrhage by cranial ultrasonography; 4) serious coexistent anomaly incompatible with long-term survival; 5) uncorrectable cyanotic heart disease by echocardiography; and 6) no "honeymoon period"(a time of adequate oxygenation after operative repair). At least one preductal PaO_2 greater than 100 Torr or one postductal PaO_2 greater than 50 Torr was required in an effort to exclude patients with unsalvagable bilateral pulmonary hypoplasia.

We have previously reported a retrospective review of neonates with pulmonary failure at the University of Michigan from 1979 to 1982 in which criteria were established that would reliably identify infants with projected mortality rates of 80–100% with conventional ventilatory support.[14-16] These specific criteria include: 1) "acute deterioration" ($PaO_2 < 40$ Torr or pH < 7.15 for longer than 2 hours); 2) Oxygenation Index (OI) > 40 on three of five measurements taken at least 30 minutes but

TABLE 2. *ECMO Indications for CDH*

1) Acute deterioration ($PaO_2 < 40$ Torr or pH < 7.15 for more than 2 hours)
2) OI > 40 on three of five measurements between 30 and 60 minutes apart

$$OI = \frac{FiO_2 \times \text{mean airway pressure} \times 100}{\text{postductal } paO_2}$$

3) Severe barotrauma

TABLE 3. *ECMO Exclusion Criteria for CDH*

1) Age > 7 to 10 days
2) Gestational age < 35 weeks
3) Pre-existing intracranial hemorrhage
4) Serious coexistent anomaly
5) Uncorrectable cyanotic heart disease
6) No "honeymoon period" (one preductal $paO_2 > 100$ Torr or one postductal $paO_2 > 50$ Torr)

no more than 1 hour apart (where MAP = mean airway pressure):

$$OI = \frac{FiO_2 \times \text{mean airway pressure} \times 100}{\text{postductal } paO_2}$$

and 3) severe barotrauma (any four of the following: pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, persistent air-leak for > 23 hours, pneumopericardium, MAP > 15 Torr).

In the absence of contraindications, infants with CDH treated after June 1981 and who met any one of these three criteria were placed upon ECMO. Survival was defined as discharge of a living child from the first hospitalization. Data was collected on pre- and postoperative care, associated anomalies, complications, and outcome. Statistical analysis was performed using Fisher's exact test.

Results

Patient Data

Between June 1974 and December 1987, a total of 59 patients with CDH were treated at the University of Michigan, C.S. Mott Children's Hospital. Nine patients were diagnosed after the first 24 hours of life and were excluded from further analysis. The remaining 50 patients were all symptomatic during the first hour of life and diagnosed correctly within the first 12 hours of life. Sixteen patients were treated before June 1981 ("pre-ECMO era," Group 1), and 34 patients were treated since that date ("ECMO era," Group 2).

Fifteen of 16 Group 1 patients were born at outlying hospitals within our usual referral area and were transferred before any operative intervention. In Group 2, 23 of 34 infants were born at outside hospitals. Five of these 23 were from beyond our usual referral area and had their diaphragmatic hernias repaired before transfer. Of these five infants, three required ECMO support, and all five survived. The increased percentage of inborn patients seen in Group 2 (eleven of 34 or 32% *vs.* one of 16 or 6%) is partially explained by the increased likelihood of prenatal discovery and transfer of the mother to our institutional high-risk obstetrical unit before delivery (nine patients).

Infants in Groups 1 and 2 were comparable with respect to EGA, birth weight, and the likelihood of primary repair of the diaphragmatic defect (Table 4). There was a higher

TABLE 4. *CDH Patient Characteristics*

Characteristics	Group 1	Group 2
Average gestational age	38.4 ± 3.4 weeks	38.3 ± 2.6 weeks
Average birth weight	3.03 ± 0.69 kg	3.09 ± 0.63 kg
Additional anomalies	12.5%	18%
Left-sided hernia	93.8%	76%
Primary repair	84.6%	88%
Age at operation	9.62 ± 5.0 hours	7.7 ± 3.7 hours

TABLE 5. *Ventilator Settings Pre- And Post-ECMO*

	Rate	PIP/PEEP	MAP	FiO_2
Mean pre-ECMO settings	100	42/4	18	100%
Mean post-ECMO settings	32	27/3	6	35%
Mean ABG before ECMO	O_2Sat = 92% $PaCO_2$ = 62 Torr PaO_2 = 52 Torr pH = 7.28			

PIP = peak inspiratory pressure.
PEEP = positive end-expiratory pressure.

proportion of right-sided hernias seen in Group 2 (24%) and more patients in Group 2 had significant additional congenital anomalies. Patients in this group tended to undergo operation earlier, although this difference did not achieve statistical significance ($p > 0.05$). In Group 2, six infants were excluded from consideration for ECMO support secondary to contraindications detailed in the Survival Data section; [of these six patients, two were excluded on the basis of chromosomal anomalies, two others were excluded because they who had no "honeymoon period," and two because of prematurity (EGA = 32 and 33 weeks, respectively)].

As indicated by a review of their records, three patients in Group 1 would have qualified for ECMO support had it been available. In Group 2, 15 patients qualified and were placed on ECMO support. Six of these infants suffered acute deterioration of their pulmonary status, and nine met OI criteria as defined above. The average age at initiation of bypass was 41 hours (range of 13–130 hours). The mean time on bypass was 137 hours, slightly less than six days. This is roughly twice the average length of time on bypass for infants with meconium aspiration at our institution. Two patients required support for greater than 200 hours, whereas four patients required less than 100 hours. Table 5 shows the mean postductal arterial blood gases (ABG) of infants before the initiation of ECMO, as well as the average ventilator settings just before and just after bypass.

The duration of hospitalization for Group 1 survivors averaged 20.5 days. In Group 2 survivors, there was no significant difference in length of stay between ECMO and non-ECMO patients at 46.1 and 43.4 days, respectively.

Survival Data

The overall survival of patients in Group 1—infants treated before the availability of ECMO—was eight of 16 (50%). Of the patients in Group 2—those infants treated since ECMO support has been available—26 of 34 (76%) infants survived to be discharged from the hospital. This difference ($p = 0.06$) did not reach statistical significance due to the small size of each group; however, a clear trend is apparent (Fig. 1).

Before 1981, two of the eight nonsurvivors of Group 1 would not have been candidates for ECMO, had it been available, based on the previously detailed exclusion criteria. Three patients died intraoperatively or before repair could be attempted. Three Group 1 patients, however, would have qualified for ECMO support, had it been available; all three died with irreversible pulmonary failure. All eight survivors in Group 1 did well, requiring ventilatory support for an average of two days after operation.

Group 2 patients can be divided into those who did or did not receive ECMO support. Thirteen of the 19 infants treated after operation with conventional methods alone survived (68%). All six patients who died had specific contraindications for the use of ECMO; two patients had chromosomal abnormalities, two had no "honeymoon period," and two were premature (Table 6).

In 15 infants whose projected mortality was greater than 80%, ECMO support was initiated in our neonatal unit after conventional mechanical ventilation failed; 13 of these patients survived (87%). The first death in this subgroup occurred in a patient who also had tetralogy of Fallot which was not appreciated on the routine pre-ECMO echocardiogram. The diagnosis was made by cardiac catheterization when the patient could not be successfully weaned from ECMO support despite apparently adequate pulmonary function. Primary operative repair of the tetralogy was performed, but the patient succumbed

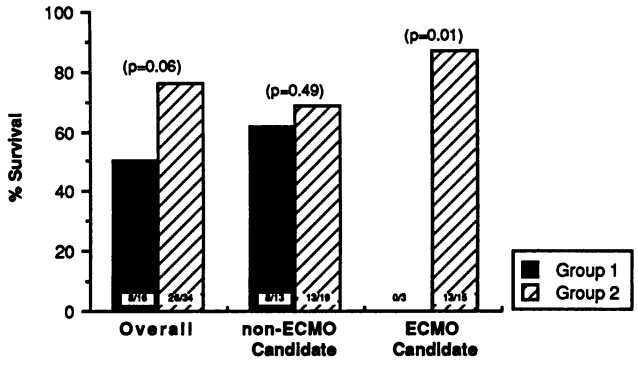

FIG. 1. Survival is shown for CDH patients in the entire series (overall survival). In addition, the survival comparison is shown for CDH patients who met ECMO inclusion criteria (ECMO candidates—see Table 2) and for those who did not (non-ECMO candidates—Table 3). The p-value in each case represents comparison of Group 1 (before ECMO became available) to Group 2 (after ECMO became available).

TABLE 6. *CDH Patients Excluded From ECMO*

Patient No.	Reason for Exclusion
1	No "honeymoon period"
2	No "honeymoon period"
3	Premature (EGA of 32 weeks)
4	Trisomy 18
5	Absent short arm of chromosome 21
6	Premature (EGA of 33 weeks)

because of postoperative intracranial hemorrhage after being on ECMO bypass for a total of 13 days. The second death occurred in an infant who was placed on ECMO at 82 hours of age by reason of OI criteria. A patent ductus arteriosus (PDA) ligation was required on the sixth day of life while on ECMO. The ECMO course concluded uneventfully after 186 hours on bypass, with the infant receiving minimal ventilatory support. During the ensuing 48 hours, persistent fetal circulation recurred, complicated by acute right heart failure. Aggressive ventilatory support was required, bronchopulmonary dysplasia developed, and the child eventually died of sepsis at 18 months of age, having been weaned successfully from ventilatory support but never having left the hospital.

Complications

All deaths in both groups, with the exception of the infant who had tetralogy of Fallot, were related to pulmonary failure. Two surviving patients in Group 1 developed small bowel obstructions requiring enterolysis.

Five complications occurred in the Group 2 survivors who did not require ECMO support. Three patients had contralateral pneumothoraces requiring thoracostomy tube placement, and two infants had evidence of mild bronchopulmonary dysplasia on follow-up x-ray studies.

In the group of patients supported with ECMO, seven had contralateral pneumothoraces (46.7%). Bleeding problems secondary to the anticoagulation necessary for use of ECMO were the most serious and frequently seen complications of this form of management (Table 7). Four infants had such complications: three patients had intracranial hemorrhage (one fatal, one resulting in significant developmental delay, and one minor intraparenchymal bleed), and one patient had hemopericardium requiring operative decompression, at which time PDA ligation was also performed. Chronic pulmonary disease was judged moderate to severe in three patients, leading in one infant indirectly to a late death at the age of one year, after having been discharged from the hospital. In three others, mild bronchopulmonary dysplasia was seen on follow-up x-rays with no clinically detectable compromise.

TABLE 7. *Complications Related to ECMO*

Complication	No. of Patients
Large volume gastrointestinal bleed due to tolazoline	1
Dislodged umbilical artery catheter with 400 cc bleed	1
Large volume chest tube bleed	1
Hemopericardium causing tamponade, requiring emergent thoracotomy	1
Intracranial hemorrhage	3 (2 major, 1 minor)

Discussion

Congenital diaphragmatic hernia may result in bilateral hypoplasia of the fetal airways and pulmonary vasculature. Ipsilateral hypoplasia is generally more severe. The physiologic consequences produce a spectrum of illness, ranging from an incidental finding on chest x-ray in an asymptomatic child to acute respiratory distress at birth manifested by hypercapnia, hypoxemia, and acidosis. Patients who present after 24 hours of life rarely have significant illness and have essentially no morbidity or mortality from operative repair. Those who present and require treatment during the first hours of life are usually severely ill and require aggressive care for salvage. Most infants of this latter group will experience a "honeymoon period." Unfortunately, many of these children develop pulmonary artery hypertension and persistent fetal circulation with right to left shunting characterized by progressive hypoxemia on maximal ventilator settings. Historically, at major centers with state-of-the-art neonatal care, the mortality for these infants has ranged from 40–60%. These figures have failed to improve over the last 20 years, despite impressive improvements in neonatal intensive care. Table 1 gives a review of our experience from 1974 to 1981 and a comparison with that of several others published during the last 20 years. Our survival rate is consistent with other large series published at that time. Despite significant changes in neonatal pulmonary and critical care, including the use of tolazoline, alkalinization by hyperventilation, paralysis, and pressure-limited ventilation, the mortality for infants with early or immediate symptoms remained approximately 50% over this 20-year period.

Keeping in mind the inherent weaknesses of retrospective studies, a simple review of the survival data from this study presents four interesting comparisons. First, a comparison of the survival of infants treated before the availability of ECMO (50%) with those of the ECMO era (76%) is not significant ($p = 0.06$). Although the 26% change suggests improvement, the sample size is currently too small to reach significance. When the survival of patients of the pre-ECMO period who would have qualified for ECMO (0 of three patients, or 0%) is compared with that of infants who were treated later and who qualified for and were treated with ECMO (13 of 15 patients, or 87%), the large difference in survival rates is significant at

p = 0.01 despite the small numbers. Third, and perhaps most importantly, a comparison of the expected mortality (80–100%) with the observed mortality (13%) in the ECMO group is highly significant at p = 0.0015. This strongly suggests that ECMO impacts favorably on survival of those infants who are the most ill and who have no contraindications to the procedure. Finally, all series will have some patients who will never be viable, regardless of the treatment. In Group 2, this number was six of 34, or approximately 18%. If these patients are excluded, the resulting survival gives an idea of the sensitivity and specificity of the selection criteria used during the ECMO era. With the exclusion of these six nonviable patients, the Group 2 survival rate reaches 93% (26 of 28 patients).

There are a number of differences in the groups included in this study. The average length of hospitalization is shorter for Group 1 patients (20.5 *vs.* 45 days). Group 2 patients managed conventionally required ventilator support for 10 days, as compared to 2 days for patients in Group 1. (ECMO patients required an average of 20 days of ventilator support.) In addition, more patients of Group 2 had additional nonpulmonary anomalies. This suggests that more critically ill patients were being cared for in the later group and that the difference in survival between Groups 1 and 2 is perhaps more impressive than was first evident. The selection criteria used for ECMO are an obvious source of bias in comparing these statistics with those of other series. The well-publicized selection criteria may prevent some patients from being referred to our center, thus resulting in a form of local selection. The incidence of fatal fetal anomalies associated with CDH ranges from 5% to 60%.[17-19] In our series, there were six infants in the post-ECMO group who had lethal anomalies that precluded ECMO (Table 6). Four of these patients had anomalies that were nonpulmonary in nature, (two patients were premature infants and two had chromosomal abnormalities), and the remaining two infants were believed to have lethal bilateral pulmonary hypoplasia because no "honeymoon period" occurred. It is the treatment of this latter group of infants that is most controversial. No clinical event or observation has been proven reliable and predictive for selecting those children who cannot be salvaged.

A recent report by Bohn et al.[20] suggests that the comparison of $PaCO_2$ and the Ventilatory Index (respiratory rate × MAP) is of prognostic value in predicting survival in a center where ECMO is not available. Using the 2-hour postoperative criteria suggested by Bohn for evaluating our eight inborn ECMO patients for whom this data could be analyzed, two of eight fell into the 100% mortality subset, and six of eight fell into the 50% mortality subset (Fig. 2). One patient from each subset died. In addition, Heaton et al.[13] have reported a 58% survival in a series of twelve patients treated with ECMO, all of whom met

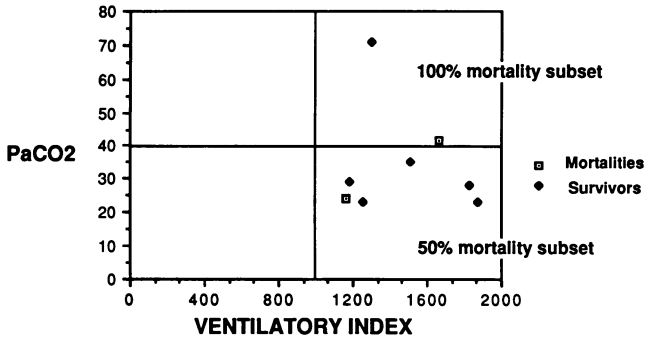

FIG. 2. Survival prediction and outcome for the eight inborn ECMO-CDH patients using the comparison of 2-hour postoperative P_aCO_2 values and Ventilatory Index recently suggested by Bohn.[20] Predicted and actual survival vary considerably, although the patient numbers are small (see text).

criteria for nonsurvival as predicted by Bohn. It would appear that these criteria may be of prognostic value when using conventional therapy, but they are not predictive in patients treated with ECMO. Currently, ECMO programs in this country use a variety of subjective and objective selection criteria. Based on the data contained in this review, we have eliminated the requirement for a "honeymoon period" in infants with CDH and currently consider ABG data an insufficiently sensitive indicator of prognosis to withhold ECMO. Table 3 (except for item six) shows our current exclusion criteria.

There are several areas of potential improvement in the care of critically ill infants with CDH using ECMO. One of these has been the antenatal ultrasonographic diagnosis of CDH and the referral of the mother to a high-risk obstetrical unit with neonatal ECMO capability. Nine such patients were seen in our series. One of these infants had contraindications to ECMO and subsequently died. Four of these were managed successfully with conventional therapy and survived. The remaining four were treated with ECMO. One of these was the sole early mortality in the ECMO group (tetralogy of Fallot); the other three patients did well. This mortality (22%) is somewhat better than that recently reported by Adzick.[21] In his report, eight of ten infants with prenatal CDH diagnosis died; four died despite treatment with ECMO. Our experience has led us to advocate the early transfer of the antepartum mother in such a circumstance to a high-risk obstetrical unit where ECMO is available to the newborn infant. In the absence of antenatal diagnosis, early transfer is desirable to avoid pre-ECMO deterioration as well as time-dependent, mechanical ventilation-induced barotrauma or bronchopulmonary dysplasia.

The imminent development of a heparin-free bypass system should decrease the complications and mortality caused by bleeding—specifically, intracranial hemorrhage. In addition, a heparin-free bypass system would allow consideration of premature infants who are of less than

35 weeks gestational age for ECMO treatment. Currently, the cumulative risks of long-term extracorporeal support revolve around bleeding complications and oxygenator failure. The heparin-bound circuit would lessen these long-term risks and potentially allow exploration of prolonged bypass in these infants.

Summary

Fifty infants with congenital diaphragmatic hernia symptomatic during the first hour of life were treated between June 1974 and December 1987. The introduction of ECMO in 1981, along with improved neonatal intensive care, was followed by an improvement in survival (from 50% to 76%) within this period. Of the ECMO era patients who failed conventional therapy and had an expected mortality of 80–100%, 13 of 15 (87%) survived, thus reversing the expected mortality. This indicates that ECMO is a successful, reliable, and safe method of pulmonary support for selected critically ill infants with congenital diaphragmatic hernia.

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