Recent Experience with Diaphragmatic Hernia and ECMO

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In the past 4 years at the Medical College of Georgia, a total of 74 patients underwent extracorporeal membrane oxygenation (ECMO) with 62 (84%) survivors. Forty-seven of these infants had meconium aspiration syndrome and 11 had diaphragmatic hernia. The use of ECMO, when indicated, after reduction and repair of the diaphragmatic hernia, results in normal oxygen delivery, allows time for pulmonary maturation, and increases survival. A total of 27 referrals for diaphragmatic hernia were studied. Six infants had surgical repair and did not require ECMO. Eleven patients, after surgical repair, were treated with ECMO and seven survived. More importantly 10 patients died before the use of ECMO. Six infants died either before or during transport from referring hospitals and four died while in the delivery room or neonatal unit before ECMO. Of these 10 infants, eight were potential candidates for ECMO. Thirteen of the twenty-seven (48%) infants survived. Seven of eleven (64%) infants who received the benefit of ECMO survived. Eight infants who met the criteria for ECMO died before its use. Had ECMO been used in those eight infants, our data suggests that at least four may have survived. The data from this report support the concept that infants undergoing surgical repair of diaphragmatic hernia, when ECMO is not available, should be referred to an ECMO center in the early postoperative period. Furthermore infants with prenatal diagnosis of diaphragmatic hernia should be delivered at a center where surgical as well as ECMO expertise are available.

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THE EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) program at the Medical College of Georgia Children's Medical Center was instituted in March 1985. While initially begun out of concern for the pulmonary problems encountered in the postoperative management of patients with congenital diaphragmatic hernias (CDH) and for other term infants with respiratory failure, it became apparent that infants with a CDH comprise only a small portion of infants eligible for this invasive procedure. In the past decade, reports of successful treatment of CDH have focused on use of ECMO with subsequent improvement in survival.[1-3] In fact, even in our initial experience of CDH treated with ECMO, we believed we had markedly changed our survival rate. After several years experience, however, we realized that a significant number of infants with CDH repair did not survive the period between repair, transfer, if necessary, and subsequent ECMO therapy. These unrecognized deaths provided the stimulus to review our series of CDH from the referring physician's initial contact to subsequent outcome.

Methods

Documents for 29 consecutive accepted referrals with CDH and 147 consecutive accepted referrals without CDH to the Medical College of Georgia ECMO Program from March 1 1985 through July 15, 1989 were reviewed. During this period 74 infants underwent ECMO, with 62 (84%) survivors. Forty-seven had meconium aspiration syndrome, 11 had CDH, 9 had persistent fetal circulation, 6 had respiratory distress syndrome/hyaline membrane disease, and 1 had congenital heart disease.

Initially 29 referrals for CDH were evaluated. Two infants were excluded from the study: an infant with profound hypoxemia secondary to uncorrectable congenital heart disease with CDH, and an infant with dysmorphic features, severe congenital heart disease, CDH, and no parental consent for treatment of the CDH. The data of the remaining 27 patients were analyzed. Twenty-four of the twenty-seven (88%) patients developed respiratory symptoms in the first 12 hours; the remaining three infants

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developed symptoms after discharge from the newborn nursery. Twenty-five of these infants had surgical repair of the CDH. Two patients, delivered in our hospital, died in the delivery room.

An abdominal incision was used for repair in 24 patients and a thoracic incision was used in one. Primary repair of the diaphragmatic defect was accomplished in 17 patients and a prosthesis (silicone elastomer or polytetrafluroethylene) was used in eight.

Eleven of the twenty-seven study patients were either delivered at our hospital or outborn and referred to our hospital for initial surgical management. The remaining 16 patients were referred for consideration of ECMO after successful surgical repair at the referring hospital.

The technique of ECMO in neonates with respiratory failure has been well described.[4] Specific criteria used to identify infants with a predicted mortality rate in excess of 80% with CDH included:

(1) $AaDO_2 > 610$ for 8 hours, or $AaDO_2 > 600$ for 12 hours ($AaDO_2 = 760 - (PaO_2(mmHg) + PaCO_2$ (mmHg) + 47), with the patient breathing 100% oxygen or FIO_2 of 1.0,
(2) acute deterioration ($PaO_2 < 40$ mmHg for > 2 hours),
(3) and oxygenation index (OI) > 40 on three of five measurements between 30 and 60 minutes apart (OI = mean airway pressure above atmosphere × FIO_2 × 100 divided by postductal PaO_2 (mmHg).

Specific criteria used to exclude infants from the use of ECMO included:

(1) estimated gestational age < 35 weeks,
(2) presence of intracranial hemorrhage,
(3) uncorrectable cyanotic congenital heart disease,
(4) severe, uncorrectable associated anomalies, and
(5) parental refusal.

The 27 infants were divided into the following groups: (1) surgery only, 6 patients not requiring ECMO; (2) ECMO survivors, 7 patients with initial surgical repair followed by ECMO; (3) ECMO deaths, 4 patients with initial surgical repair followed by death during or immediately after ECMO; and (4) pre-ECMO deaths, 8 patients with initial surgical repair followed by ECMO referral with death in transport or on arrival to our NICU, and 2 infants with antenatal diagnosis who died at delivery in our hospital. Data examined for each patient included sex, estimated gestational age (EGA), birth weight (BW), side of defect, prosthesis, and antenatal diagnosis. We also analyzed $PaCO_2$ (mmHg) and ventilation index (VI; mean airway pressure × respiratory rate) before surgery and $PaCO_2$ (mmHg) and VI before ECMO.[5] Our third set of parameters included highest pre- and postductal PaO_2 (mmHg) after surgery, $AaDO_2$ before ECMO, age of patient (hours) at ECMO (or death), and time on ECMO (hours). Survivors, with and without ECMO (groups 1 and 2), and nonsurvivors (groups 3 and 4), with and without ECMO were studied by chi square, analysis of variance using 1 and 2 factors, unpaired t test, and a stepwise discriminant analysis.

Results

Thirteen of twenty-seven (48%) infants survived. Of the ECMO deaths (group 3), 2 were due to intracranial hemorrhage, 1 due to pulmonary hypoplasia/pulmonary hypertension, and 1 due to cardiomyopathy/pulmonary hypertension. Of the pre-ECMO deaths (group 4), 7 were due to respiratory failure/pulmonary hypertension, 2 due to pulmonary hypoplasia/pulmonary hypertension, and 1 due to respiratory failure/pulmonary hypertension and esophageal atresia/tracheoesophageal fistula.

Of 11 patients either delivered at our hospital or referred for CDH repair, eight (73%) survived. Five infants with antenatal diagnosis of CDH were attended at delivery by the authors, and two died within the first 30 minutes of life. The other three infants had successful repair, required ECMO, and two survived.

Of the 16 infants referred for ECMO after CDH repair, five (31%) survived. Eleven referrals for ECMO died: 3 during or immediately after ECMO, 6 before or during transport, and 2 shortly after arrival to our neonatal intensive care unit.

Statistical analysis of the four groups revealed no significant difference between the survivors (groups 1 and 2) and nonsurvivors (groups 3 and 4) with respect to sex, EGA, BW, side of defect, prosthesis, and antenatal diagnosis (Tables 1 and 2). However the unpaired t test comparing sex *versus* BW revealed that male infants were significantly larger than female infants (3.1 kg *versus* 2.7 kg; $p < 0.04$). Further analysis of the groups comparing survivors with nonsurvivors revealed no difference in $PaCO_2$ (mmHg) and VI before surgery, and $PaCO_2$ (mmHg) and VI before ECMO (Table 3). Analysis of the groups comparing highest pre- and postductal PaO_2 (mmHg) after surgery, $AaDO_2$ before ECMO, age at onset of ECMO (or death), and duration of ECMO revealed no statistical differences (Table 4). An interesting result was the mean age

TABLE 1. *Comparison of Demographic Data by Groups*

Groups	No.	Sex	EGA* (Weeks)	Birth* Weight (Kg)
		Male/Female		
1	6	4/2	37 ± 3	2.95 ± 0.60
2	7	3/4	40 ± 2	3.12 ± 0.67
3	4	0/4	38 ± 2	2.58 ± 0.25
4	10	4/6	39 ± 2	2.83 ± 0.47

* Shown for EGA and Birthweight is mean ± SD.

TABLE 2. *Comparison of Side of Defect, Use of Prosthesis, and Antenatal Diagnosis by Groups*

Groups	No.	Side Left/Right	Prosthesis	Antenatal Diagnosis
1	6	4/2	0	0
2	7	6/1	2	2
3	4	3/1	2	1
4	10	8/2	4	2

of death in group 4 (excluding the two delivery room deaths) of 26.8 hours (range, 7.5 to 60 hours).

Calculation of actual and predicted survivals plotting $PaCO_2$ (mmHg) *versus* VI (Bohn's criteria)[5] revealed a 49% predicted survival rate before surgery in groups 2 and 3. Our actual survival rate was 64%. Similar calculations before ECMO for groups 2 and 3 revealed a 14% predicted survival rate as compared to a 64% actual survival rate. Of the eight patients in group 4, use of Bohn's criteria predicted 19% survival before surgery and 12% survival before ECMO.

A stepwise discriminant analysis, including all variables except time on ECMO and age of ECMO, was used to distinguish the group memberships. Only two variables, VI before surgery and use of prosthesis, entered the discriminant analysis at $p < 0.05$. The prosthesis distinguished between those patients receiving surgery only and those also requiring ECMO. The VI functioned to distinguish between all groups. The resulting discriminant formula was applied to the 10 patients in the pre-ECMO death group (group 4). Two infants died in the delivery room. The remaining eight infants were potential ECMO candidates. Based on statistical analysis, four of these eight patients clearly would have been predicted to survive with ECMO. These 4 predicted survivors would increase the survival of infants referred for ECMO from 31% (5 of 16) to 56% (9 of 16). Furthermore the remaining four infants would have had an approximate 50-50 chance of survival. These additional two predicted survivors would potentially increase the survival of infants referred for ECMO from 56% (9 of 16) to 69% (11 of 16), essentially the same survival rate as our population who were either delivered at our hospital or referred for surgical repair of the CDH.

Discussion

In 1946 Gross[6] reported the successful repair of CDH in seven children, including one infant who was less than 24 hours of age. This heralded a period of optimism surrounding the treatment of neonates with diaphragmatic hernia. The concept that postdelivery respiratory failure was secondary to compromise of pulmonary function by expanding viscera in the chest indicated an obvious emergency. Early and aggressive surgical management of these infants was thus necessary if survival were to result.

Aggressive surgical management initially resulted in improved survival, but despite refinement in surgical techniques, the mortality rate for infants with this lesion remained 50% or higher.[7] Most frustrating was the apparent successful surgical repair of this abnormality with marked improvement in pulmonary function as measured by oxygenation, only to be followed by progressive and often catastrophic deterioration and death. This deterioration was presumed secondary to progressive pulmonary hypertension and right to left shunting with severe hypoxemia. The medical management of this complication (hyperventilation, volume support, and pharmacologic agents) was not a panacea.[8]

Since the initial reports[1-3] of the benefit of ECMO in CDH were published, ECMO centers have reported favorable results. Recent reports, however, have emphasized the inherent mortality of the infant with CDH despite ECMO availability.[9,10] One subgroup of infants with such circumstances is the infant with antenatal diagnosis that does not survive the delivery room resuscitation. This subgroup with CDH may only survive if treated with fetal surgery, the prospects for which are unknown.[11,12] A second group of infants with an inherent mortality risk are those who survive the delivery room resuscitation, continue in extremis, and can only be managed successfully with immediate ECMO and delayed surgical repair of the CDH.[13] A third group of infants with an unacceptable mortality risk is our previously undescribed group of infants who have had successful surgical repair of the CDH. A period of time elapses that may include a 'honeymoon period,' progressive deterioration, and the infant's death either before or during transport. These hopeless cases

TABLE 3. *Comparison of $PaCO_2$ and VI Before Surgery and ECMO by Groups*

Groups	No.	$PaCO_2$ Before Surgery	VI Before Surgery	$PaCO_2$ Before ECMO	VI Before ECMO
1	6	35 ± 20	513 ± 192		
2	7	41 ± 22	1593 ± 616	51 ± 17	2013 ± 376
3	4	52 ± 4	1025 ± 206	62 ± 26	1895 ± 474
4	10*	53 ± 20	1607 ± 460	68 ± 43	1818 ± 351

Shown for $PaCO_2$ and VI is mean ± SD. $PaCO_2$ is expressed as mm Hg.

* Two patients died before measurements being obtained.

TABLE 4. *Comparison of Pre- and Postductal PaO_2 After Surgery, $AaDO_2$ Before ECMO, Age on ECMO (death), and Time on ECMO*

Groups	No.	Highest Preductal PaO_2 After Surg	Highest Postductal PaO_2 After Surg	$AaDO_2$ Before ECMO	Age on ECMO (Hours)	Time on ECMO (Hours)
2	7	265 ± 178	134 ± 125	644 ± 24	40 ± 31	156.9 ± 46.3
3	4	216 ± 133	73 ± 39	654 ± 26	35 ± 25	210.5 ± 113.9
4	10*	176 ± 110†	114 ± 112	621 ± 27	21 ± 20	—

PaO_2, $AaDO_2$, age on ECMO and time on ECMO are mean ± SD. PaO_2 is expressed as mm Hg.

* Two infants had no values obtained because they died in the delivery room.

† Only six infants in group 4 had preductal values obtained.

may have resulted in significant mortality that is potentially reversible.

Significant pulmonary hypertension with secondary vasoconstriction is not the sole cause of pulmonary deterioration. Morphologic and physiologic studies have implicated pulmonary hypoplasia as a major contributing factor to the mortality of these infants. Stolar et al.[2] have suggested that ECMO in a patient with a PCO_2 (mmHG) value of more than 50 Torr or a highest pre- or postductal PaO_2 (mmHg) of less than 100 may be contraindicated. Bohn et al.[5] reported a useful technique of predicting survival in patients before surgery that is related to an index of alveolar ventilation. His formula plots $PaCO_2$ (mmHg) *versus* VI and classifies patients into one of four groups. When this formula was applied to our patients before surgery, it was relatively accurate at predicting the subsequent survival rate of the patients who required surgery only. However when the $PaCO_2$ (mmHg) and VI values before ECMO were plotted using his criteria, there was a marked discrepancy between actual and predicted survival. Heiss et al.[14] have reported that Bohn's criteria may be useful or of prognostic value if ECMO is not available, but they can not be used reliably in patients treated with ECMO. Newman et al.[15] have recently noted many previously reported categories of high mortality rate (best preductal PaO_2 (mmHg) of less than 100, early prenatal diagnosis, prosthesis repair, and Bohn's 100% predicted mortality) may have a successful outcome when ECMO was used. Based on these reports and our experiences, we believe the infant who survives the delivery room resuscitation and the surgical repair of the CDH is an ECMO candidate.

Selective use of ECMO has probably excluded some infants who were potential survivors. Expedient transfer of the patient to an ECMO center before deterioration (whether it be before or after surgery) is of paramount importance. Hestitation or delay in transfer should be avoided. Our data demonstrate that of the 10 patients in our series who did not receive the potential benefit of ECMO, two were nonviable from the beginning. However eight patients were acceptable candidates for ECMO. Of these eight potential candidates, statistical analysis suggests that six of these infants may have survived. In fact the mean age of death in these eight infants was 26.8 hours, more than adequate time for repair, transfer, and potential ECMO. The data of Weber[9] support this concept because he clearly states that no parameter in his study could predict death in their ECMO patients and, therefore, no patient should be excluded from repair or from ECMO. The obvious exclusion criteria in our study was the death of the patient either before or during transport.

The concept of antenatal diagnosis of diaphragmatic hernia has fascinating implications. The capability of *in utero* transfer to the ECMO center reduces the potential morbidity and mortality of transport from an outlying hospital. Although the infant arrives at the ECMO center transported *in utero*, this does not guarantee survival. Adzick et al.[11] reported that 8 of 10 infants with *in utero* transport died. Heiss et al.,[14] in contrast, reported that seven of nine (78%) survivors who were transported *in utero* survived.

In our series five infants had the antenatal diagnosis of diaphragmatic hernia. Of these five, three underwent ECMO after surgical repair, with two infants surviving. Two infants died while in the delivery room.

We believe that our data support the concept that infants undergoing surgical repair of a diaphragmatic hernia where ECMO is not available should be transferred to an ECMO center in the early postoperative period. Furthermore we believe that infants with the prenatal diagnosis of diaphragmatic hernia should be delivered at a center where surgical and ECMO expertise is available.

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Discussion

DR. J. ALEX HALLER, JR. (Baltimore, Maryland): First I would like to correct Dr. Walter Merrill retrospectively to his earlier paper because his statement that 43% of Americans will reach 80 years of age is untrue because he apparently is not considering babies under 1 month of age as Americans! If they are included, less than 43% will achieve 80 years of age because those statistics by the various life insurance companies do not include babies under 1 month of age. Thus the other frontier, not old age but newborn, is the one that Dr. Howell and his associates have brought to our attention.

He was kind enough to provide the manuscript to me several weeks ago, which has given me the opportunity to become more nervous about what I might like to say, but more importantly, he has given me a time to have some of our statisticians look at his complicated data.

Our statisticians indicate that his figures are correct.

Dr. Howell's thesis is an important one, that all babies who have a diagnosis of congenital diaphragmatic hernia before or after birth should be managed in neonatal surgical centers where ECMO is available.

Does his data support that thesis? It has a profound impact on many very fine surgeons in this auditorium who can certainly close holes in the diaphragm!

Is there a significant advantage to having such babies in neonatal units where intensive care and other forms of support are routinely available to them?

This technology called extracorporeal membrane oxygenation, has, I believe, been looking for a disease for many years! Whether it has found it yet remains to be seen.

Most of Dr. Howell's patients were being treated for meconium aspiration syndromes. Life-threatening meconium aspiration reflects poor obstetrical care, and therefore, I think an important adjunct to this proposal that there be in the same ECMO centers, excellent obstetrical programs, including continuous medical education to decrease this preventable complication.

How about babies with congenital diaphragmatic hernia? He has shown us that with the use of this ECMO technology, there is better than a 50% survival rate, but just barely better. When Dr. Robert Gross first reported his series in the 1940s from the Boston Children's Hospital, there was a 50% survival rate! Many things have changed since then because many of Dr. Gross' patients survived longer than 24 hours in outlying areas and selected themselves as survivors. Dr. Gross noted that the real challenge was in those babies less than 24 hours of age, the group in which Dr. Howell is using ECMO.

Technically more than one third of Dr. Howell's patients required the use of a prosthetic material in the repair in the hole in the diaphragm, which is more than most of us have in our own experience. What are your indications, Dr. Howell, for the use of prosthetic material?

What would be the outcome of these children in your region who had the repair of their diaphragmatic hernias in outlying hospitals if they did not require referral to you? In other words, you have shown us that those babies who came late or after operative repair have a much higher mortality rate. Do you know how many children at the same time were operated on successfully in those same centers and who were not referred to you? That is a statistic that we did not hear and the one that would convince me that your thesis is correct.

Finally, what are you doing about regional leadership in all aspects of this prenatal and postnatal diagnosis? Do you have in place a regional system that brings the high-risk pregnant mother into your center to make available to them as early as possible these modern forms of technology?

Have you indicated to the various referring hospitals that your team is ready? What do you believe is the responsibility of a neonatal surgeon in such a regional program?

DR. KEITH E. GEORGESON (Birmingham, Alabama): When you consider what Dr. Haller just mentioned that 30 years ago the mortality rate was reported as 50% and more recently that mortality rate has been climbing, it is refreshing to hear a paper describe a technique that is reversing that trend.

The reason that ECMO is successful, I believe, is because oxygen is a potent pulmonary vasodilator and most of our congenital diaphragmatic hernia patients die of persistent pulmonary hypertension.

We have been extremely impressed with the efficacy of ECMO as well, and for the last 2 years have been using a slightly different protocol. Instead of immediate repair of the diaphragmatic hernia, we have delayed repair depending on conventional medical management and ECMO to stabilize the patient. Those patients who stabilize with conventional management are managed with ECMO. Those patients who do not stabilize are placed on ECMO once they meet criteria.

Using this protocol and taking patients who are symptomatic immediately at birth, that is they are cyanotic right at birth, we have taken a mortality rate that was initially 80% and dropped it to 45%.

Do you have exclusion criteria or do you put all patients who have reached your center on ECMO if they meet the criteria? In other words, do you exclude nonresponders from ECMO?

Have you ever repaired any of your patients while on ECMO, and do you think there is any place for this technique?

Wouldn't you prefer to have the patients referred to you before hernia repair? When we were reviewing our own patients, we found that we had lost a number in the operating room or before going to the operating room, just from logistical delays.

What percentage of your patients do you think have such profound pulmonary hypoplasia that they would not respond to ECMO?