Congenital Diaphragmatic Hernia

Stabilization and Repair on ECMO

KEVIN P. LALLY, M.D., MICHAEL S. PARANKA, M.D., JAY RODEN, M.D., KEITH E. GEORGESON, M.D., JAY M. WILSON, M.D., CRAIG W. LILLEHEI, M.D., CHARLES W. BREAUX, JR., M.D., MICHAEL POON, M.D., REESE H. CLARK, M.D., and JAMES B. ATKINSON, M.D.

Availability of extracorporeal membrane oxygenation (ECMO) support and the potential advantages of delayed repair of congenital diaphragmatic hernia (CDH) have led several centers to delay CDH repair, using ECMO support if necessary. This study reviews the combined experience of five ECMO centers with infants who underwent stabilization with ECMO and repair of CDH while still on ECMO. All infants were symptomatic at birth, with a mean arterial oxygen pressure (Pa_{O_2}) of 34 mmHg on institution of bypass despite maximal ventilatory support. A total of 42 infants were repaired on ECMO, with 18 (43%) surviving. Seven infants had total absence of the diaphragm, and 28 required a prosthetic patch to close the defect. Only five infants ever achieved a best postductal Pa_{O_2} over 100 mmHg before institution of ECMO. Prematurity was a significant risk factor, with no infants younger than 37 weeks of age surviving. Significant hemorrhage on bypass was also a hallmark of a poor outcome, with 10 of the 24 nonsurvivors requiring five thoracotomies and six laparotomies to control bleeding, whereas only one survivor required a thoracotomy to control bleeding. In follow-up, nine of the 18 survivors (50%) have developed recurrent herniation and seven (43%) have significant gastroesophageal reflux. Importantly, five of the 18 survivors were in the extremely high-risk group who never achieved a Pa_{O_2} over 100 mmHg or an arterial carbon dioxide pressure ($PaCO_2$) less than 40 mmHg before the institution of ECMO. In conclusion, preoperative stabilization with ECMO and repair on bypass may allow some high-risk infants to survive. Surviving infants will require long-term follow-up because many will require secondary operations.

From the Departments of Surgery and Pediatrics, Wilford Hall USAF Medical Center, San Antonio, Texas; the Departments of Surgery, the Children's Hospital of Alabama, Birmingham, Alabama; Children's Hospital Medical Center, Boston, Massachusetts; Presbyterian Hospital and the Children's Medical Center of Dallas, Texas; and the Children's Hospital of Los Angeles, Los Angeles, California

CONGENITAL DIAPHRAGMATIC HERNIA (CDH) continues to be a vexing problem for the surgeon. Despite dramatic improvements in neonatal surgery, anesthesia, and intensive care, mortality rates through the mid-1980s remained around 30% to 50% in most reported series.[1-3] The widespread availability of extracorporeal membrane oxygenation (ECMO) improved survival statistics in several series, up to 75% to 80%.[4,5] Not all centers, however, have seen this significant improvement in survival.[6] Of note, several ECMO centers used exclusionary criteria in the patients with CDH, thereby avoiding ECMO in the highest-risk patients.[7,8] There also remained a group of patients who could not be salvaged despite ECMO therapy after operation, some of whom did not survive long enough after emergent operation to be placed on ECMO. During this period of increasing availability of ECMO, Sakai and colleagues[9] found that thoracic compliance worsened rather than improved after repair and suggested that infants with CDH might be better managed by delaying operation for a time while the infant was stabilized. Their patients were as old as 92 hours of age before undergoing repair of the diaphragmatic hernia. Others showed no apparent worsening of survival with the delayed approach; however, in these series, patients who did not "stabilize" were excluded from operation and died.[10] Recently, Nakayama et al.[11] showed that respiratory system compliance improved using a delayed approach to infants with CDH. In centers with ECMO capability, delayed operation with preoperative stabilization, using ECMO if necessary, became a potential alternative in managing the extremely high-risk infant with CDH. Connors et al.[12] reported a series of six patients using delayed repair on ECMO, with four of their patients surviving. We report a multi-institutional experience of

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Address reprint requests to Kevin P. Lally, M.D., Division of Pediatric Surgery, UTHSC Houston, 6431 Fannin, Suite 6-264, Houston, TX 77030.

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42 patients with CDH who underwent preoperative stabilization using ECMO and delayed repair while still on bypass.

Materials and Methods

A retrospective review of all patients with CDH who underwent preoperative ECMO with repair while on bypass was performed. Data collected included demographics such as age and sex, indications for ECMO, arterial blood gases, operative course, blood product requirements, complications, and outcome.

All involved ECMO centers used a delayed approach to patients with CDH with stabilization before repair. Patients who remained unstable (persistent hypoxemia, acidosis, or hypotension) were considered ECMO candidates. Each center has individual criteria to place a patient on ECMO, although they fall into one of several categories as outlined in Table 1. No patient with CDH was excluded from ECMO on the basis of poor arterial blood gas values.

Patients were cannulated using a right neck incision with insertion of internal jugular venous and carotid arterial catheters. All patients were maintained on venoarterial ECMO. The patients were anticoagulated with heparin to maintain the activated coagulation time in the 180- to 200-second range. After institution of bypass, patients underwent operative repair at varying times in the ECMO course. The diaphragmatic hernia was either repaired early, within the first 24 to 48 hours, later, when the patient was ready for decannulation, or after the patient demonstrated an inability to wean from ECMO. All patients were repaired through a transabdominal approach, and a chest tube was placed in the ipsilateral thorax.

The patients were divided into survivors and nonsurvivors. The data for survivors and nonsurvivors were analyzed using the Kruskal Wallis analysis of variance, the unpaired, two-tailed t test, and Fisher's exact test where appropriate. Significance was assumed with a p value of <0.05.

Results

A total of 42 patients were treated in five centers. There were at least seven other infants seen in the five centers who did not meet ECMO criteria due to prematurity and died shortly after birth.

TABLE 1. *Criteria for ECMO*

a $ADO_2 > 610$ for > 8 hr
Oxygenation index > 40 for ≥ 2 hr
Acute deterioration
Barotrauma
Cardiac arrest or failure

TABLE 2. *Demographic Data**

	Survivors	Nonsurvivors	p
Estimated gestational age (wk)			
Mean ± SD	40 ± 2	37 ± 2	<0.001†
≤37	0/18	10/24 (42%)	<0.002‡
Left-sided hernia	11/16 (69%)	19/24 (79%)	NS‡
Prenatal diagnosis	5/17 (29%)	8/18 (44%)	NS‡
Mean birth weight (±SD)	3.3 kg ± 0.3	2.8 kg ± 0.5	<0.01†

* Not all patients had all data available.
† Unpaired t test.
‡ Fisher's exact test.

Overall survival was 43%, or 18 of 42 patients. One patient was placed on ECMO but was not repaired because he was thought to be nonsalvageable after further evaluation. The severity of illness is demonstrated by the fact that virtually every infant was symptomatic at birth. The indications for bypass varied among centers, but most patients had either an oxygenation index (mean airway pressure × fractional inspired oxygen (FIO_2) × $100/Pa_{O_2}$) over 40 or acute deterioration as the indication for ECMO.

Although infants with obvious chromosomal anomalies were excluded from ECMO, six patients had associated congenital cardiac anomalies (two patients with a ventricular septal defect, one each with an anomalous coronary artery, hypoplastic heart, atrioventricular canal, and hypoplastic aorta arch). All of those infants died.

No blood gas value present before bypass was able to predict death with 100% accuracy. Although inability to achieve a postductal $Pa_{O_2} > 100$ was present in 94% of infants dying, most of the survivors (81%) also never achieved a postductal $Pa_{O_2} > 100$. Overall, the survivors had a significantly higher best postductal Pa_{O_2} (median, 58) than the nonsurvivors (median, 37) ($p < 0.05$). Of note, five of the surviving infants also never achieved a $PaCO_2 < 40$. Evaluating survival by the ventilation index (ventilator rate × mean airway pressure) was not possible in all cases because some patients were treated with high-frequency oscillatory ventilation.

Seven (17%) of the infants in this series had total absence of the diaphragm (six nonsurvivors, one survivor), and a total of 28 infants (67%) required insertion of a polytetrafluoroethylene patch as a diaphragm substitute. Nine of the 18 survivors (50%) were known to have developed a late recurrent hernia. Seven of the nine infants with recurrent herniation were initially repaired with a patch.

Demographic data are outlined in Table 2. Most nonsurvivors were younger than 40 weeks' gestational age, and 42% were younger than 37 weeks (Fig. 1) ($p < 0.001$). Only six (33%) of the survivors were younger than 40 weeks gestational age, and none were younger than 37 weeks. Characteristics of the ECMO run are outlined in

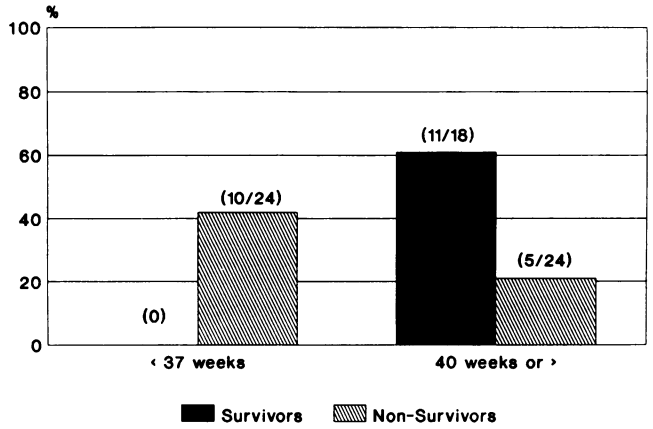

FIG. 1. Survival by gestational age. Numbers in parenthesis represent the actual number of patients.

Table 3. Only three surviving infants required an ECMO run of greater than 216 hours (or 9 days), as opposed to 20 nonsurvivors ($p < 0.001$).

The complications were significantly greater in the nonsurviving infants (Table 4). The average number of complications in the survivors was 1.2, whereas nonsurvivors had a mean of 1.7 complications per patient. Complications included sepsis, intracranial hemorrhage, renal failure, bowel necrosis, liver failure, and recurrent hernia in two of the nonsurvivors.

Blood loss in the nonsurviving infants was occasionally prodigious, with five infants requiring more than 800 mL/kg of blood, and one infant requiring more than 2000 mL/kg during the ECMO course (Table 5). Sixty-one per cent of the surviving infants required less than 200 mL/kg total blood during the entire ECMO run, whereas only 4% of the nonsurvivors required less than 200 mL/kg of blood. Conversely, 63% of the nonsurvivors required more than 600 mL/kg blood, and only 28% of the survivors required more than 600 mL/kg blood (Fig. 2). A total of five thoracotomies and six laparotomies were needed in 10 of the nonsurviving infants in an attempt to control hemorrhage (Table 5). The laparotomies in all patients were thought necessary because of abdominal tamponade.

TABLE 3. *ECMO Run Parameters*

	Survivors	Nonsurvivors	p
Oxygenation index (mean ± SD)	50 ± 17	58 ± 23	NS*
Age at cannulation (hr) median	9	8	NS*
Duration of ECMO RUN (hr)	191	339	<0.001*
ECMO run >216 hr (9 days)	3/18 (17%)	20/24 (83%)	<0.001†
ECMO run >336 hr (14 days)	1/18 (6%)	12/24 (50%)	<0.003†
Age at CDH repair (hr)	113	124	ND†
ECMO run after repair (hr)	89	231	<0.001†

* Kruskal-Wallis with unpaired t test.
† Fisher's exact test.

TABLE 4. *Nonhemorrhagic Complications in Survivors* Versus *Nonsurvivors*

	Survivors	Nonsurvivors
Recurrent herniation	9 (50%)	2 (8%)
Neck wound infection	2 (11%)	0
Acute renal failure	1 (6%)	5 (21%)
Sepsis	0	3 (13%)
Chylothorax	1 (6%)	0
Intestinal necrosis	1 (6%)	1 (4%)
Supraventricular tachycardia	3 (17%)	1 (4%)
Other	5 (28%)	5 (21%)

One survivor required a thoracotomy to control bleeding from the chest tube. Several of the other survivors had incisional or chest tube bleeding, but none required reoperation ($p < 0.01$). There was no significant difference in blood loss (expressed as mL/kg/hour) between patients undergoing operation early (<72 hours) in the ECMO run *versus* later.

Discussion

The apparent failure to improve the survival rate in published series of patients with congenital diaphragmatic hernia through the mid-1980s has been attributed by some to the fact that referral centers were seeing increasingly sicker patients who previously did not survive to be transported. Some recent series, however, have demonstrated improved survival, which was attributed to the availability of ECMO.[13,14] There remained, however, a problematic group of infants who either did not survive to operation, who died immediately after operation before ECMO support could be instituted, or who died after decannulation after a successful ECMO course. The simultaneous broader acceptance of a delayed approach to repair of congenital diaphragmatic hernia and ECMO availability prompted several centers to use ECMO to stabilize the patient with congenital diaphragmatic hernia who failed conventional support.[12,15,16] This series and others was composed of the infants who could not be stabilized without ECMO. It should be emphasized that the 43% survival rate is not reflective of all infants with CDH, but only those sick enough to require ECMO support. The severity of the disease in the infants in this series is highlighted by the fact that all were symptomatic immediately on

TABLE 5. *Bleeding Complications*

	Survivors	Nonsurvivors
Hemothorax	2 (11%)	10 (42%)
Hemoperitoneum	0	6 (25%)
Intracranial hemorrhage	1 (6%)	5 (21%)
Neck wound bleeding	2 (11%)	2 (8%)
Other bleeding	1 (6%)	3 (13%)

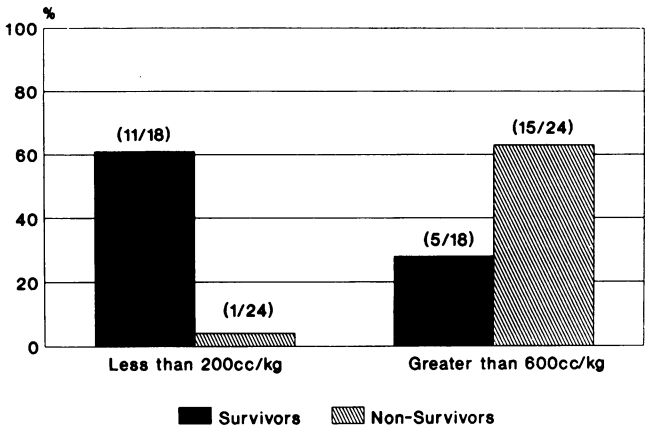

FIG. 2. Blood loss in survivors *vs.* nonsurvivors. Numbers in parenthesis represent the actual number of patients.

clamping the umbilical cord, at least seven had total agenesis of the diaphragm, 28 infants required a patch to close the defect, and the mean arterial Pa_{O_2} on institution of bypass was 34 mmHg. The surviving infants had a significantly higher best postductal Pa_{O_2}; however, as others have mentioned previously, predicting survival solely on the basis of the postductal arterial Pa_{O_2} is difficult.[5,17] Indeed, only five of the 18 (28%) surviving infants ever achieved a postductal Pa_{O_2} over 100 mmHg. The combined inability to ventilate ($PaCO_2 > 40$ mmHg) or oxygenate (postductal $Pa_{O_2} < 100$ mmHg) carries a very poor prognosis.[6,18] Importantly, at least five infants in this series survived despite never achieving a best postductal Pa_{O_2} over 100 or a $PaCO_2$ less than 40, suggesting a potential survival benefit to this approach.

Prematurity was a significant risk factor. Only two survivors (11%) were 37 weeks estimated gestation, and none were less than 37 weeks, whereas 14 nonsurvivors (58%) were 37 weeks or less. Although no infant was excluded from ECMO if he or she met standard criteria, at least seven patients, not included in the data analysis, were not placed on ECMO because of severe prematurity (<34 weeks), and all died within hours. Most centers do not exclude the premature over 34 weeks of gestation from ECMO; nonetheless, preterm delivery is clearly an important risk for death.

Not surprisingly, the ECMO course and postoperative course for these infants had a large number of complications. Only one infant (2%) had no complications. Hemorrhage of some kind was present in 60% of the patients in this series, and significant bleeding was a hallmark of a poor outcome. Fifteen of the nonsurvivors (63%) had major hemorrhage; either intracranially, or significant enough to require laparotomy or thoracotomy for control. Only one survivor required reoperation for hemorrhage, and one had a small intracranial hemorrhage. The significant bleeding in these patients has prompted most centers to delay repair until later in the ECMO course, preferably when the patient is close to minimal or "rest" settings on bypass. This, it is hoped, would allow for decannulation and reversal of heparin shortly after repair. Meticulous hemostasis with the liberal use of electrocautery, application of fibrin glue, minimal dissection, maintenance of platelet counts above 100,000/mm^3, and minimal anticoagulation with activated coagulation times below 200 seconds are all helpful adjuncts.

The ECMO course for the nonsurvivors was dramatically longer than for the survivors. Only three (18%) survivors required a run of more than 9 days, whereas most (83%) of the nonsurvivors did. Of note, only one survivor was kept on ECMO over 14 days compared with 12 of the nonsurvivors. Most nonsurvivors were decannulated either because complications occurred, or it was thought that ECMO offered no further benefit. This would warrant a close re-evaluation of the patient's status and likely prognosis 9 days into the ECMO course. A frank appraisal of the likelihood of success would be appropriate at between 9 and 14 days.

It is important to note that the surviving infants often have other problems. A large number of the infants required a patch to close the diaphragmatic defect. This patch can pull away with growth or potentially cause chest wall deformity, and indeed, 50% of the survivors have developed recurrent herniation to date. Although some type of prosthesis is the only reasonable alternative in the infant on bypass, because of the potential for prohibitive bleeding from an extensive flap dissection, subsequent revisions can be anticipated as the infant grows. Gastroesophageal reflux and esophageal dysmotility have become increasingly recognized as associated problems in patients with congenital diaphragmatic hernia requiring ECMO.[19,20] At least seven (39%) of the survivors had clinically significant gastroesophageal reflux, with three requiring a fundoplication. Given the potential for long-term problems, these children require close follow-up as they grow.

It is apparent from this study and others that, despite the availability of immediate cardiopulmonary support and prolonged extracorporeal bypass, some infants have an inadequate amount of functional lung tissue to survive. The options currently available for these infants are limited. Very early prenatal diagnosis with fetal repair has been performed; however, patient selection is appropriately strict.[21] Which of those patients who undergo fetal repair might be salvageable without fetal repair, using ECMO support after birth, is unknown. Regardless, fetal correction is irrelevant for most patients with CDH, because the diagnosis is made either late in gestation or after delivery. In some patients who fail to respond, lung transplantation might be a potential option. Lobar lung transplantation has been performed successfully in an animal

model, but there has yet to be a report of a successful transplant in an infant.[22] Whole-lung transplantation is problematic in the newborn because there is an extreme shortage of donors. Some type of transplant, however, may be the only option in the infant with an inadequate amount of lung tissue to survive.

In conclusion, preoperative stabilization with repair on ECMO may offer some survival benefit in an extremely high-risk group of infants. Whether ECMO is best used before, during, or after operation, which patients will need lung transplantation and timing of operation will require further studies. Although some infants are salvageable with immediate ECMO support, the potential for recurrent herniation, late death, and gastroesophageal reflux is high. Because of these problems, long-term follow-up of these patients is essential.

References

1. Nguyen L, Guttman FM, De Chadarevian JP, et al. The mortality of congenital diaphragmatic hernia: is total pulmonary mass inadequate, no matter what? Ann Surg 1983; 198:766–770.
2. Mishalany GH, Nakada K, Woolley MM. Congenital diaphragmatic hernias: eleven years' experience. Arch Surg 1979; 114:1118–1123.
3. Anderson KD. Congenital diaphragmatic hernia. *In* Welch KJ, Randolph JG, Ravitch MM, O'Neill JA, Rowe MI, eds. Pediatric Surgery, 4th Edition. Chicago: Yearbook Medical Publishers, 1986:589–601.
4. Weber TR, Connors RH, Pennington DG, et al. Neonatal diaphragmatic hernia: an improving outlook with extracorporeal membrane oxygenation. Arch Surg 1987; 112:615–618.
5. Howell CG, Hatley RM, Boedy RF, et al. Recent experience with diaphragmatic hernia and ECMO. Ann Surg 1990, 211:793–798.
6. O'Rourke PP, Lillehei CW, Crone RK, Vacanti JP. The effect of extracorporeal membrane oxygenation on the survival of neonates with high risk congenital diaphragmatic hernia: 45 cases from a single institution. J Pediatr Surg 1991; 26:147–152.
7. Stolar C, Dillon P, Reyes C. Selective use of extracorporeal membrane oxygenation in the management of congenital diaphragmatic hernia. J Pediatr Surg 1988; 23:207–211.
8. Heiss K, Manning P, Oldham KT, et al. Reversal of mortality for congenital diaphragmatic hernia with ECMO. Ann Surg 1989; 209:225–230.
9. Sakai H, Tamura M, Hosokawa Y, et al. Effect of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. J Pediatr 1987; 111:432–438.
10. Hazebroek FWJ, Tibboel D, Bos AP, et al. Congenital diaphragmatic hernia: Impact of preoperative stabilization. A prospective pilot study in 13 patients. J Pediatr Surg 1988; 23:1139–1146.
11. Nakayama DK, Motoyama EK, Tagge EM. Effect of preoperative stabilization on respiratory system compliance and outcome in newborn infants with congenital diaphragmatic hernia. J Pediatr 1991; 118:793–799.
12. Connors RH, Tracy T, Bailey PV, et al. Congenital diaphragmatic hernia repair on ECMO. J Pediatr Surg 1990; 25:1043–1047.
13. Langham MR, Krummel TM, Greenfield LJ, et al. Extracorporeal membrane oxygenation following repair of congenital diaphragmatic hernias. Ann Thorac Surg 1987; 44:247–252.
14. Bailey PV, Connors RH, Tracy TF, et al. A critical analysis of extracorporeal membrane oxygenation for congenital diaphragmatic hernia. Surgery 1989; 106:611–616.
15. Truog RD, Schena JA, Hershenson MB, et al. Repair of congenital diaphragmatic hernia during extracorporeal membrane oxygenation. Anesthesiology 1990; 72:750–753.
16. Breaux CW Jr, Rouse TM, Cain WS, Georgeson KE. Improvement in survival of patients with congenital diaphragmatic hernia using a strategy of delayed repair after medical and/or extracorporeal membrane oxygenation stabilization. J Pediatr Surg 1991; 26: 333–338.
17. Newman KD, Anderson KD, Van Meurs K, et al. Extracorporeal membrane oxygenation and congenital diaphragmatic hernia: should any infant be excluded? J Pediatr Surg 1990; 25:1048–1053.
18. Breaux CW, Jr, Rouse TM, Cain WS, Georgeson KE. Congenital diaphragmatic hernia in an era of delayed repair after medical and/or extracorporeal membrane oxygenation stabilization: a prognostic and management classification. J Pediatr Surg 1992; 27:1192–1196.
19. Stolar CJH, Levy JP, Dillon PW, et al. Anatomic and functional abnormalities of the esophagus in infants surviving congenital diaphragmatic hernia. Am J Surg 1990; 159:204–207.
20. Taylor GA, Short BL. Esophageal dilatation and reflux in neonates on extracorporeal membrane oxygenation after diaphragmatic hernia repair. Am J Roentgenol 1988; 151:1055.
21. Harrison MR, Adzick NS, Longaker MT, et al. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. N Engl J Med 1990; 322:1582–1584.
22. Crombleholme TM, Adzick NS, Hardy K, et al. Pulmonary lobar transplantation in neonatal swine: a model for treatment of congenital diaphragmatic hernia. J Pediatr Surg 1990; 25:11–18.