Improving Survival for Patients With High-Risk Congenital Diaphragmatic Hernia by Using Extracorporeal Membrane Oxygenation

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● The benefit of extracorporeal membrane oxygenation (ECMO) in cases of high-risk congenital diaphragmatic hernia (CDH) was studied by comparing pre-ECMO (1987-1990) and post-ECMO (1991-1994) 3-month survival statistics. Fifty-five CDH patients who presented in respiratory distress within 6 hours after birth were referred—18 in the pre-ECMO era and 37 in the ECMO era. During the entire study period (December 1987 through July 1994) the patients were treated by the same protocol of preoperative stabilization and delayed surgery; the only difference was the addition of ECMO beginning in January 1991. The patients were stratified based on the response to conventional treatment: 1, no response (irretrievable); 2, stable; 3, unstable. The 3-month survival rate for the unstable neonates (who could not be stabilized by conventional therapy) improved from 0% (0 of 9) in the pre-ECMO era to 61% (11 of 18) in the ECMO era (*P* = .004). This highly significant difference shows that ECMO is a very valuable addition to the management of high-risk CDH patients whose conditions remain unstable despite maximal conventional therapy.
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INDEX WORDS: Congenital diaphragmatic hernia, extracorporeal membrane oxygenation.

D ESPITE ADVANCES in neonatal care, including prenatal diagnosis, neonatal transport, intensive care treatment, anesthesiology, and surgery, the mortality rate among infants with congenital diaphragmatic hernia (CDH), treated by conventional ventilatory management and pharmacological support, remains high. The reported mortality rate for high-risk patients who have symptoms within 6 hours after birth ranges from 29% to 80%.[1-9] Extracorporeal membrane oxygenation (ECMO) was introduced as a therapy for newborns with respiratory failure unresponsive to maximal conventional treatment and may be used to support neonates who have respiratory distress caused by CDH.[10-12]

A number of investigators have reported success in treating CDH with ECMO.[2-4,13-16] However, others have not seen improvement with use of ECMO.[17,18] According to the Extracorporeal Life Support Organization (ELSO) registry, the survival rate for CDH patients treated by ECMO is 58%.[19] This suggests that ECMO has no significant impact on the survival of newborns with high-risk CDH.

In the present report we evaluate the role of ECMO in the management of CDH at our institution.

MATERIALS AND METHODS

All patients with CDH who were symptomatic within 6 hours after birth and who were referred between December 1987 and July 1994 were included in the study. All patients were treated by a protocol of delayed surgery after preoperative stabilization.[5-8] When ECMO became available in our institution (in January 1991), it was incorporated into this protocol for CDH, whether preoperatively or postoperatively. ECMO was offered after conventional ventilatory and medical management had failed, if the patient fulfilled the entry criteria for ECMO, if there were no contraindications for ECMO, and if parental consent was obtained. No infant in this study was excluded from ECMO support on the basis of failure to achieve a minimum PaO_2 before the institution of ECMO.

Venoarterial ECMO was used as previously described by Bartlett et al.[12] If ECMO was required for preoperative stabilization, the diaphragmatic defect was repaired during ECMO, at the end of the run, if the patient could be weaned from ECMO support.[20] ECMO was discontinued when respiratory failure resolved (gas exchange requiring PIP of less than 30, ventilator rates of less than 40, and FiO_2 of less than 0.50) or when a complication arose that required cessation of ECMO (such severe bleeding complications rendering a contraindication to continued heparinization). Survival is defined as "alive at the age of 3 months." Survival statistics were compared for two time periods: (1) December 1987 through December 1990, when ECMO was not available and all children were treated with conventional ventilatory support and pharmacological management (the pre-ECMO era, n = 18), and (2) January 1991 through July 1994, when ECMO was available and was used if conventional treatment failed (the ECMO era, n = 37).

The children were classified into the three groups described below.

"Irretrievable" patients. These patients were (1) newborns with severe respiratory distress, noted immediately after birth, in whom a reasonable or normal gas exchange was never reached, despite endotracheal intubation and artificial ventilation, and who died within 2 hours after birth, before ECMO could be initiated, (2) newborns who died before or during transportation (pre-ECMO era, n = 1; ECMO era, n = 7), or (3) newborns with a severe congenital anomaly (especially chromosomal) for whom not all therapeutic modalities were offered (pre-ECMO era, n = 1).

Conventionally stabilized patients. These were newborns with high-risk CDH, who recovered well by (maximal) conventional treatment and who underwent surgical repair of their diaphragmatic defect after conventional stabilization. They never met

ECMO-entry criteria before repair of their diaphragmatic defect (pre-ECMO era, n = 7; ECMO era, n = 12).

Unstable patients. These were newborns with high-risk CDH, and who could not be stabilized by maximal conventional treatment and who met one or more ECMO-entry criteria (pre-ECMO era, n = 9; ECMO era, n = 18). The patients in this category were subdivided into those who did (a) or did not (b) receive ECMO support.

We made this stratification because we wanted to evaluate the effect of ECMO on survival. The irretrievable patients were in such distress that ECMO could not be initiated before death or before severe brain damage had occurred. In these circumstances any therapy, which ever applied, is doomed for failure. The availability of ECMO equipment had no effect on survival, neither in this group nor in the conventionally stabilized patients. Because no patient in the latter category met the ECMO-entry criteria and nearly all patients survived, ECMO is not a therapeutic option for this group. Thus, only in the unstable patients could the effect of the availability of ECMO equipment be measured. For comparisons of survival rates, the two-sided Fisher's Exact test was used.

RESULTS

Fifty-five newborns with high-risk CDH were evaluated—18 in the pre-ECMO era (Fig 1) and 37 in the ECMO era (Fig 2).

One patient in the pre-ECMO era was categorized as "irretrievable" because of a chromosomal anomaly. One neonate in the first period and seven in the latter period were irretrievable; they died of severe respiratory distress shortly after birth, before ECMO could be or could have been initiated. In this category, the average transcutaneous oxygen saturation was 64%, the average PaO$_2$ was 4.5 kilo-Pascals (kPa) (34 mm Hg), the average PaCO$_2$ was 10.9 kPa (82 mm Hg), and the average pH was 6.89.

In the pre-ECMO period, preoperative stabilization could be achieved by conventional treatment (CT) in seven patients (Fig 1). In these patients the diaphragmatic defect could be repaired, and six survived. Nine patients could not be stabilized conventionally; none of them had surgical repair, and none
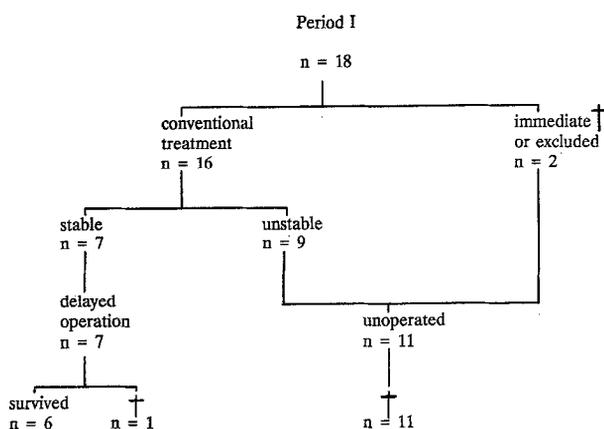
Period I

n = 18

conventional treatment n = 16   immediate or excluded n = 2

stable n = 7   unstable n = 9

delayed operation n = 7   unoperated n = 11

survived n = 6   n = 1   n = 11

Fig 1. Progress of 18 high-risk CDH patients in the pre-ECMO era (December 1987 through December 1990).

Period II

n = 37

conventional treatment n = 30   immediate n = 7

stable n = 12   unstable n = 18

ECMO n = 16   no ECMO n = 2

delayed operation n = 12   operated on ECMO n = 15   cessation ECMO n = 1   unoperated n = 10

stable n = 11   unstable n = 1

ECMO n = 1

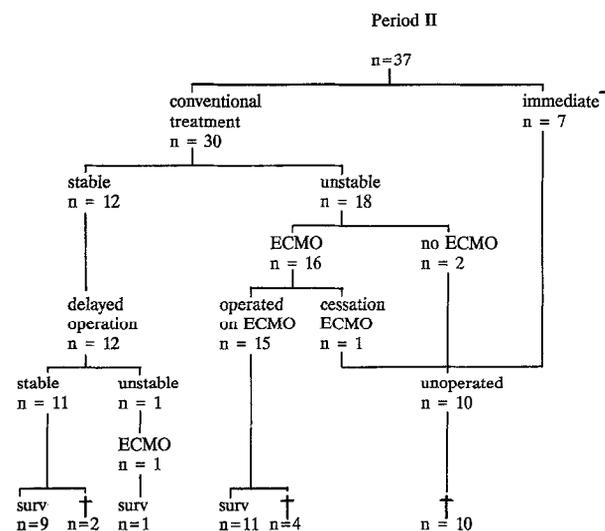surv n=9   n=2   surv n=1   surv n=11   n=4   n = 10

Fig 2. Progress of 37 high-risk CDH patients in the ECMO era (January 1991 through July 1994).

survived. These patients would have qualified for ECMO support had it been available.

Since ECMO became available at our institution, preoperative stabilization by conventional therapy could be achieved in 12 patients (Fig 2). All 12 had repair of their diaphragmatic defect, and 10 survived, although postoperative ECMO support was required for one of them.

Eighteen cases were refractory to conventional management and were considered for ECMO treatment. In two of the patients, ECMO therapy was not instituted; in one patient ECMO treatment was refused by the parents, and in the very first patient, who was an ECMO candidate, we thought it was better to repair the diaphragmatic defect before initiation of ECMO, during preparation of the ECMO circuit. Both patients died. Thus, in 16 patients ECMO was used for preoperative stabilization. In one patient the ECMO treatment was discontinued because of severe cerebral bleeding, and the patient died without having repair of the diaphragmatic defect. The other 15 patients could be weaned from ECMO, and all had repair of their diaphragmatic defect during ECMO, late in the ECMO run. Eleven survived. The four deaths after ECMO were related to multiorgan failure (n = 1), severe lunghypoplasia (n = 1), or recurrent persistent pulmonary hypertension (n = 2). The demographic data of the different patient groups, for the two time periods, are reported in Table 1.

The overall survival rate was 33% in the pre-ECMO era and 57% in the ECMO era. Excluding the irretrievable patients in both periods, the survival rate

Table 1. Demographic Data for Both Time Periods

	Irretrievable		Conventionally Stable		Unstable	
	Pre-ECMO	ECMO	Pre-ECMO	ECMO	Pre-ECMO	ECMO
Male:female ratio	0:2	4:3	3:4	5:7	5:4	10:8
Gestational age (wk)						
Average	42.0	38.7	38.5	38.0	40.3	39.8
Range	(42-42)	(36-42)	(34-41)	(34-42)	(38-42)	(34-42)
Birth weight (g)						
Average	2,850	2,740	2,780	2,660	3,160	3,410
Range	(2,300-3,400)	(1,500-3,460)	(1,480-3,500)	(1,760-3,740)	(2,450-3,930)	(2,560-4,175)
Apgar scores (average & range)						
1 min	1.5 (1-2)	1.8 (1-4)	7.4 (4-9)	5.0 (3-9)	4.5 (1-9)	3.2 (0-6)
5 min	2.5 (1-4)	3.8 (2-6)	6.0 (4-9)	6.7 (4-10)	4.8 (1-8)	4.8 (0-8)
Side						
Left:right	2:0	5:2	5:2	10:2	8:1	16:2

NOTE: Pre-ECMO era, December 1987 through December 1990; ECMO era, January 1991 through July 1994.

was 38% in the first period and 70% in the second period (Fisher's Exact test, $P = .08$). The survival rate among infants who could be stabilized conventionally was 86% in the pre-ECMO era and 83% in the ECMO era (Fisher's Exact test, $P > .50$). The survival rate for the conventionally not-stabilized patients was 0% in the first period and 61% in the latter period (Fisher's Exact test, $P = .004$).

Ultimately, 11 of the 16 unstable patients who were supported by ECMO survived (69%), whereas no unstable patient survived without ECMO support (Fisher's Exact test, $P = .0006$).

DISCUSSION

In this report we present our experience with 48 severely afflicted infants with CDH, who were treated according to a protocol of preoperative stabilization and delayed surgery.[5-9] This protocol was unchanged during the entire period of the study.

The only difference in management was the addition of ECMO for (pre- or postoperative) stabilization since January 1991. This offers the opportunity to evaluate the role of ECMO in the treatment of high-risk CDH, by dividing the patients into two groups with respect to ECMO availability (pre-ECMO and ECMO).

The overall survival rate for high-risk CDH patients increased from 33% in the pre-ECMO era to 57% in the ECMO era. This means improvement, but the difference is not significant statistically. For this reason, and because infants with CDH have gained less advantage by ECMO than have infants with respiratory distress from other causes,[19] the benefits of ECMO support for high-risk CDH patients remain controversial.[2-4,13-18] However, to assess the impact of ECMO we must compare identical populations with respect to demographic data as well as severity of disease, because differences in the composition of the

groups can influence the outcome. Over the past decade, many attempts have been made to grade the seriousness of the disease and to establish criteria by which survival could be predicted or by which patients could be considered for a certain kind of (aggressive) therapy. Parameters used, are the interval from birth until the appearance of symptoms; the occurrence of a "honeymoon period"[21]; and blood-gas analysis, with and without linkage with ventilator settings and time, eg, $AaDo_2$, oxygenation index, and ventilation index linked with $Paco_2$.[9,22-28]

Nevertheless, all criteria appear to be unreliable; there is no single, simple objective criterion by which the clinical course and outcome can be predicted and by which the two interrelated pathophysiological mechanisms (lung hypoplasia and pulmonary hypertension) can be unraveled.[4,14-16,28-31] In the literature there is agreement that neonates who are in respiratory distress within 6 hours after birth constitute a high-risk group. We divided this high-risk group into three subgroups, based on the clinical course at the time (maximal) conventional treatment was applied.

Some patients are considered to be irretrievable because they are unable to attain satisfactory oxygenation despite maximal conventional therapy immediately begun after birth. These patients have not even the ability to meet standard ECMO criteria because of lack of time. They die before ECMO can be initiated. Most investigators report only a few such cases, but these comprise 19% of the CDH patients referred to our institution in the ECMO era. This group reflects the impact of the availability of ECMO on referral patterns, but this group has a negative influence on the overall survival rate, which can lead to misinterpretation of the efficacy of ECMO treatment in CDH patients. The amount of functional lung tissue in these infants is inadequate for survival. Since January 1991, 14 infants were transferred, pre- or

postnatally, specifically for ECMO. Two could be treated conventionally, nine received ECMO support, and three died before ECMO could be initiated.

In other patients, respiratory distress can be alleviated by immediate applied conventional therapy. Some such patients can be stabilized by conventional ventilatory management and never meet ECMO-entry criteria. Others cannot be stabilized conventionally and meet standard ECMO criteria. Only in this latter group of patients can a reliable judgment be made of the benefit of ECMO for CDH.

In both periods the conventionally stabilized patients and the unstable patients were comparable with respect to gestational age, birth weight, gender distribution, Apgar scores, and side of the defect (Table 1). As might be expected, the survival rate of category II patients was virtually the same in both periods—86% in the pre-ECMO era and 83% in the ECMO era. However, the survival rate for unstable patients is significantly better in the ECMO era than it was beforehand (61% v 0%). Because the groups are comparable for both time periods, and because the only difference in treatment is the addition of ECMO in the latter period, the better survival rate can be attributed completely to ECMO therapy.

All children who had stabilization with ECMO survived; this represents an increase in the overall survival rate. All unstable children who met ECMO entry criteria died without ECMO support.

The fact that all children who met ECMO criteria died without ECMO support is in accordance with the aim of ECMO as a treatment of last resort, ie, only applied in critically ill infants, whose projected mortality rate was more than 80%.

From the experience with high-risk CDH patients treated in our institution by a protocol of delayed surgery after preoperative stabilization, with and without ECMO, we draw the following conclusions. (1) The overall mortality rate among high-risk CDH patients is still high. (2) Some infants have such severe lung hypoplasia that they were unable to attain sufficient gas exchange to bridge the time until initiation of ECMO. (3) Use of ECMO support is an improvement in our therapy protocol for cases that cannot be stabilized by conventional treatment; the survival rate associated with ECMO (61%) is significantly better than that without ECMO (0%). (4) ECMO availability changed the referral pattern; increasingly sicker patients are seen, who previously would not have survived.

REFERENCES

1. Goh DW, Drake DP, Brereton RJ, et al: Delayed surgery for congenital diaphragmatic hernia. Br J Surg 79:644-646, 1992

2. Atkinson JB, Ford EG, Humphries B, et al: The impact of extracorporeal membrane support in the treatment of congenital diaphragmatic hernia. J Pediatr Surg 26:791-793, 1991

3. Breaux CW, Rouse TM, Cain WS, et al: Improvement in survival of patients with congenital diaphragmatic hernia utilizing a strategy of delayed repair after medical and/or extracorporeal membrane oxygenation stabilization. J Pediatr Surg 26:333-338, 1991

4. Heaton JFG, Redmond CR, Graves ED, et al: Congenital diaphragmatic hernia: Improving survival with extracorporeal membrane oxygenation. Pediatr Surg Int 3:6-10, 1988

5. Cartlidge PHT, Mann NP, Kapila L: Preoperative stabilisation in congenital diaphragmatic hernia. Arch Dis Child 61:1226-1228, 1986

6. 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 23:1139-1146, 1988

7. Langer JC, Filler RM, Bohn DJ, et al: Timing of surgery for congenital diaphragmatic hernia: Is emergency operation necessary? J Pediatr Surg 23:731-734, 1988

8. Charlton AJ, Bruce J, Davenport M: Timing of surgery in congenital diaphragmatic hernia. Low mortality after preoperative stabilisation. Anaesthesia 46:820-823, 1991

9. Breaux CW, Rouse TM, Cain WS, et al: Congenital diaphragmatic hernia in an era of delayed repair after medical and/or extracorporeal membrane oxygenation stabilization: A prognosis and management classification. J Pediatr Surg 27:1192-1196, 1992

10. Hardesty RL, Griffith BP, Debski RF, et al: Extracorporeal membrane oxygenation: Successful treatment of persistent fetal circulation following repair of congenital diaphragmatic hernia. J Thorac Cardiovasc Surg 81:556-563, 1981

11. Bartlett RH, Gazzaniga AB, Huxtable RF, et al: Extracorporeal circulation (ECMO) in neonatal respiratory failure. J Thorac Cardiovasc Surg 74:826-833, 1977

12. Bartlett RH, Gazzaniga AB, Toomasian J, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure: 100 cases. Ann Surg 204:236-245, 1986

13. Weber TR, Connors RH, Pennington DG, et al: Neonatal diaphragmatic hernia: An improving outlook with extracorporeal membrane oxygenation. Arch Surg 122:615-618, 1987

14. Van Meurs KP, Newman KD, Anderson KD, et al: Effect of extracorporeal membrane oxygenation on survival of infants with congenital diaphragmatic hernia. J Pediatr 117:954-960, 1990

15. Heiss K, Manning P, Oldham K, et al: Reversal of mortality for congenital diaphragmatic hernia with ECMO. Ann Surg 209:225-230, 1989

16. Bailey PV, Connors RH, Tracy FT Jr, et al: A critical analysis of extracorporeal membrane oxygenation for congenital diaphragmatic hernia. Surgery 106:611-616, 1989

17. O'Rourke PP, Lillehei CW, Crone RK, et al: 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 26:147-152, 1991

18. Wilson JM, Lund DP, Lillehei CW, et al: Delayed repair and preoperative ECMO does not improve survival in high-risk congenital diaphragmatic hernia. J Pediatr Surg 27:368-375, 1992

19. ECMO Registry Report of the Extracorporeal Life Support Organization. International Summary, July 1994

20. vd Staak F, Geven W, Oeseburg B, et al: Experience with delayed repair of congenital diaphragmatic hernia during extracorporeal membrane oxygenation in a European center. Pediatr Surg Int 8:187-190, 1993

21. Collins DL, Pomerance JJ, Travis KW, et al: A new approach to congenital posterolateral diaphragmatic hernia. J Pediatr Surg 12:149-156, 1977

22. Raphaely RC, Downes JJ: Congenital diaphragmatic hernia: Prediction of survival. J Pediatr Surg 8:815-823, 1973

23. Boix-Ochoa J, Peguero G, Seijo G, et al: Acid-base balance and blood gases in prognosis and therapy of congenital diaphragmatic hernia. J Pediatr Surg 9:49-57, 1974

24. Bohn DJ, James I, Filler RM, et al: The relationship between $PaCO_2$ and ventilation parameters in predicting survival in congenital diaphragmatic hernia. J Pediatr Surg 19:666-671, 1984

25. Manthei U, Vaucher Y, Crowe CP: Congenital diaphragmatic hernia: Immediate preoperative and postoperative oxygen gradients identify patients requiring prolonged respiratory support. Surgery 93:83-87, 1983

26. O'Rourke PP, Vacanti JP, Crone RK, et al: Use of the postductal PaO_2 as a predictor of pulmonary vascular hypoplasia in infants with congenital diaphragmatic hernia. J Pediatr Surg 23:904-907, 1988

27. Redmond C, Heaton J, Calix J, et al: A correlation of pulmonary hypoplasia, mean airway pressure and survival in congenital diaphragmatic hernia treated with extracorporeal membrane oxygenation. J Pediatr Surg 22:1143-1149, 1987

28. Wilson JM, Lund DP, Lillehei CW, et al: Congenital diaphragmatic hernia: Predictors of severity in the ECMO era. J Pediatr Surg 26:1028-1034, 1991

29. vd Staak FHJ, Thiesbrummel A, de Haan AFJ, et al: Do we use the right entry criteria for extracorporeal membrane oxygenation in congenital diaphragmatic hernia? J Pediatr Surg 28:1003-1005, 1993

30. Marsh TD, Wilkerson SA, Cook LN: Extracorporeal membrane oxygenation selection criteria: Partial pressure of arterial oxygen versus alveolar-arterial oxygen gradient. Pediatrics 82:162-166, 1988

31. Langham MR, Krummel TM, Bartlett RH, et al: Mortality with extracorporeal membrane oxygenation following repair of congenital diaphragmatic hernia in 93 infants. J Pediatr Surg 22:1150-1154, 1987