Congenital Diaphragmatic Hernia: Mortality Determinants in a Hispanic Population.

PEDRO SERRANO, MD; GLORIA REYES, MD; HUMBERTO LUGO-VICENTE, MD*

Objectives. **Determine which factors were associated with mortality in our patients, specifically whether ventilatory parameters and arterial blood gas could be used to predict outcome. The role of delaying surgery and the presence of contra lateral pneumothorax were also assessed.**

Background. **Mortality among babies born with congenital diaphragmatic hernia remains high. The associated pulmonary hypoplasia and hypertension account for most of the overall mortality. There is no uniform consensus as to which parameters predict outcome.**

Method. **Study population consisted of thirty-two patients with CDH managed during a ten-year period. Retrospective data obtained included: perinatal data, postnatal complications, ventilatory parameter data, arterial blood gas, type and age of surgery. Ventilatory index, oxygenation index and arterial to alveolar oxygen difference (A-aDO_2) within the first 24 hours of life and after surgical correction were compared among the 23 patients who underwent surgical correction. Timing of surgery and frequency of pneumothorax were compared between survivors and non-survivors. Epi-Info Software Package was used for statistic analysis.**

Results. **Overall survival was 40%. Survival of surgically corrected infants was 61%. Non-survivors had significantly higher A-aDO_2 than survivors ($p<0.05$). No significant differences in pCO_2, ventilatory index, or oxygenation index were identified between survivors and non survivors. Surgical repair performed after the first twenty-four hours of life, was associated with a higher survival rate ($p<0.05$). Fourteen patients (39%) developed contralateral pneumothorax, eleven (79%) of these died.**

Conclusions. **(1) contralateral pneumothorax was associated with higher mortality, 2) A-aDO2 was a better prognostic indicator than pCO_2, ventilatory index, or oxygenation index, 3) delaying surgical repair was associated with better survival rate.** *Key words: Congenital diaphragmatic hernia, Mortality, Hispanic.*

Congenital diaphragmatic hernia (CDH) is a common malformation reported in one in 3500 to 4000 live births (1,2). In spite of modern advances in the management of critically ill newborn infants, mortality from CDH remains between 25% to 80% (3,10, 26). Pulmonary hypoplasia and pulmonary hypertension account for most causes of deaths, even after successful surgical repair. Different ventilatory and blood gas parameters have been used to predict outcome, but there is no uniform consensus as to which parameter is optimal (4-6). Barotrauma is also been considered an important risk factor in mortality and morbidity; although, it's contribution to mortality has not been clearly elucidated (7-10).

Delaying surgical repair until the patient is hemodynamically stable is currently advocated (11-13). Two randomized trials, comparing early versus delayed repair have failed to demonstrate significant differences in outcome (13,14). Current opinion is that surgery should be performed when the pulmonary vascular tone has been maximally stabilized, irrespective of time (8,13-18). Optimal time for surgical repair still remains controversial.

The purpose of this study was to determine: 1) factors associated with mortality, specifically whether ventilatory parameters and arterial blood gas could be use as outcome predictors, 2) define the role of barotrauma in the incidence of mortality and, 3) determine whether delayed repair improves survival.

From the Department of Pediatrics, Neonatal-Perinatal Medicine Section, University Pediatric Hospital, University of Puerto Rico, Medical Sciences Campus and the *Department of Surgery, Pediatric Surgery Section, University of Puerto Rico, Medical Science Campus.

Address for correspondence: Gloria Reyes, M.D. Department of Pediatrics, Neonatal-Perinatal Medicine Section, University of Puerto Rico School of Medicine, PO Box 365067, San Juan, Puerto Rico 00936-5067 Tel (787) 754-4064; Fax (787) 758-5307 E-Mail gloriareyes@pol.net

Materials and Methods

Patient population. Thirty-nine patients with CDH were admitted to the Neonatal Intensive Care Unit of the University Pediatric Hospital from 1985 to 1994. Thirty-six medical records were reviewed, eighteen females and eighteen males. Mean birth weight of the patients was 2.77±0.15 kg and mean gestational age was 37.4±0.5 weeks. Thirty-one (86%) patients had a defect on left side, four (11%) on the right, and one was bilateral. Fifteen infants (42%) were inborn and 21 (58%) outborn. Four patients had associated lethal anomalies and were excluded from the study. All patients developed respiratory symptoms within the first six-hours of life. Initial management in all cases (except three who required only oxygen supplementation), were paralysis and hyperventilation to keep pCO_2 below 40 mm Hg. No patient was referred for extracorporeal membrane oxygenation (ECMO).

Surgery was undertaken after achieving hemodynamic stability, regardless of patient's age. Nine patients (39%), who were never stable enough to undergo surgery, died within the first 24 hours of life. Five of these patients had severe pulmonary hypoplasia at autopsy and four had pneumothorax.

Perinatal data (birth weight, gestational age, antenatal diagnosis, place of birth, sex, Apgar scores, and use of inotropic medication), postnatal complications, and surgical management were compared between survivors and non-survivors. Ventilatory parameters, arterial blood gas (ABG), ventilatory index (VI= MAP x RR), oxygenation index (OI=MAP x FiO_2 x 100/ pO_2), and arterial-alveolar oxygen difference (A-aDO_2=[713-$PaCO_2$]/0.8-PaO_2) within the first 24 hours of life and after surgical correction were also compared. Epi-Info Statistic Software Package (CDC, Atlanta) was used for analysis of the data. Specific statistic used were: Fisher exact test, student t-test, Mann-Whitney test, and Krustal-Wallis where appropriate. Probabilities less than 0.05 was considered statistically significant. Results are expressed as mean plus or minus standard deviation.

Results

Overall survival rate was 44% (14/32). Survival among those who underwent surgery was 61% (14/23). Perinatal data can be appreciated in Table 1. Infants with antenatal diagnosis and infants born at our institution had significantly higher mortality rate than those referred from other institutions. Survivors had better Apgar scores than non-survivors.

A total of twenty-three patients (72%) underwent surgical repair. Of these, 80%(18/23) had primary closure and 20% (5/23) required a prosthetic patch. No statistical differences in survival rates were observed between infants who underwent primary closure versus patch repair (61% vs 75%). There was no significant difference in either preoperative pCO_2, OI, or VI between survivors and non-survivors . Survivors had significantly higher A-aDO2 than non-survivors (See Table 2). Survival rate of infants who underwent late surgical repair was significantly better than those who were operated early (89% vs 42%). Early operations were undertaken within the first 24 hours of age (9.8±3.6 hours), delay surgery was undertaken after 24 hours of age (46.6±25 hours).

Table 1. Perinatal Data

	Survivors n=14	Non-survivors n=18	P Value
Birth weight (kg)	3.2±0.9	2.6±0.9	NS
Gestational age (wk.)	38.5±1.7	36.8±3.4	NS
Apgar (5 min)	7±1	6±2	<0.05
Sex (M:F)	9:5	4:5	NS
Inborn	2 (14%)	9 (50%)	<0.05
Prenatal diagnosis	1(7%)	7 (39%)	<0.05

Values are mean ± SD

Table 2. Clinical data of patients who underwent surgical correction.

	Survivors n=14	Non-survivors N=9	P Value
Birth weight (kg)	3.2±0.9	3.0±0.9	NS
Gestational age (wk.)	38.5±1.7	37.2±3.1	NS
Apgar (5 min)	7±1	6±1	<0.05
Sex (M:F)	9:5	4:5	NS
Inborn	2 (14%)	3 (33%)	NS
Type of surgery			
Primary repair	11 (75%)	8 (85%)	NS
Patch repair	3 (25%)	1(15%)	NS
pCO_2	31.3"9.7	26.5±8.4	NS
OI	7.1±12.1	7.8±8.6	NS
VI	618.3±338	980±513	NS
A-aDO_2	277.6±133	442±153.3	<0.05

Values are mean ± SD

Infants who underwent late surgical repair were significantly smaller than those who were operated early. Ventilatory outcome predictors (VI, OI or $AaDO_2$) or type of procedure showed no difference between infants who underwent early or late repair (Table 3).

Fourteen patients (44%) developed contralateral pneumothorax and 10 (71%) of these died. There was no difference in mortality whether pneumothorax occurred before or after surgery (75% vs 67%). Four (29%) patients with pneumothorax never achieved hemodynamic stability and died before surgery.

Table 3. Clinical Data: Early vs. Delayed Repaired Group

	Early repair n=14	Delayed repair n=9	P Value
Birth weight (kg)	3.4±0.8	2.6±0.8	<0.05
Gestational age (wk.)	38.2±2.2	37.5±2.8	NSS
Sex (M:F)	9:5	4:5	NSS
Apgar (5 min)	6.2±1.5	7.1±1.4	NSS
Age surgery (hrs)	9.8±3.6	46.6±25.2	< 0.05
Pneumothorax	8 (57%)	2 (22%)	NSS
Preop OI	10.6±10.2	8.6±12.9	NSS
Preop VI	776±372	476±290	NSS
Preop $AaDO_2$	467±205	355±183	NSS
Survival	6(42%)	8(89%)	<0.05

Values are mean ± SD

Discussion

We have found an overall survival rate of 44% in newborn infants with CDH between 1985-1994 at our institution. Among those who underwent surgery, survival rate was 61%. Mortality of infants with CDH continues to be high despite the introduction of aggressive therapeutic modalities such as nitric oxide, high frequency oscillatory ventilation (HFOV), ECMO, exogenous surfactant, and liquid ventilation. HFOV and liquid ventilation seem promising; although, more clinical trials are needed (19-25). The use of ECMO in infants with CDH continues to be an issue of much debate. Although, it appears to have a strong role in preoperative stabilization, recent reports cast doubt as to the effect of either ECMO or HFOV in improving outcome (7,26). Success of the different therapeutic modalities will depends on the selection of candidates with sufficient lung tissue for adequate gas exchange to occur. Survival in our patients is similar to that of other centers; although, it is widely agreed that comparison of retrospective data between centers is difficult to assess (1-3, 7, 26). Some centers, using less aggressive modes of ventilation have reported survival rates as high as 75%, but more realistic investigators place survival at 50% (11,13, 7, 26).

Arterial blood gas and ventilatory parameters have been used to predict outcome (7-9). Bohn et al, reported 90% mortality when the A-aDO2 was greater than 300 mm Hg . He predicted mortality after developing quadrants combining pCO_2 and VI and predicted a mortality over 80% with oxygen index over 40 (5). None of these parameters proved to be useful in our population. In fact, A-aDO2 above 400 mm Hg appeared to be a useful predictor of poor outcome in our population.

It is well known that over distention of the lungs, induced by aggressive mechanical ventilation, leads to increase pulmonary resistance, which in turn may contribute to lung damage and air leaks (7,8). In addition, lung tissue damage is enhanced in the presence of different grades of pulmonary hypoplasia which is usually present in infants with CDH, in particular those who develop respiratory symptoms shortly after birth. Srouji et al reported a 60% incidence of contralateral pneumothorax after using conventional ventilation (7). Although mechanical ventilation with low inspiratory pressures and short inspiratory times is advocated, clearly barotrauma continues to contribute to morbidity and mortality in infants with CDH. De La Hunt et al reported ten late deaths in his series of patients, four of which died with pneumothorax (14). The group from Boston considered that 25% of the mortality of infants with CDH, prior to the adoption of strategies aimed at lung preservation, was caused by iatrogenic barotrauma (10). Therefore, techniques to reduce barotrauma, namely, permissive hypercapnia and avoidance of paralyzation, have been advocated (6,8,10,15). In fact, some centers have been able to dramatically reduce their mortality with the use of permissive hypercapnia and preoperative ECMO (5,18,20,21). Barotrauma, represented by the high incidence of pneumothorax, was higher when compared to other centers, and contributed to the mortality rate of our population. This high incidence of air leaks has been associated with the use of high inspiratory pressures needed to achieve a low PCO2 during hyperventilation. It has also been related to the use of conventional mechanical ventilation with paralyzation (5).

Emergency repair of CDH was standard therapy until 1985 when Sakai et al considered that timing of surgical repair should be carefully considered and repair should not be done on an emergency basis. A period of stabilization increases likelihood of survival, since it allows for better pulmonary mechanics and reduction of pulmonary vascular resistance. The latter, necessary to be attained, before cardio-respiratory stability can occur. Immediate repair has been associated with decreased lung compliance; therefore, increasing pulmonary morbidity (16,17,24). Delayed surgical repair is currently advocated; although, what constitutes delayed surgery has not been clearly defined yet (11-14). Poor ability of patients with CDH to respond to hemodynamic stabilization measures has been recognized as evidence of marked pulmonary hypoplasia incompatible with life (10,13). Therefore, although the method of delaying surgical repair is currently recommended, it is not an alternative in patients with severe lung underdevelopment. Delaying surgery until the patient is stable is a method of patient selection. Current consensus is to defer surgery until there is evidence of decreased pulmonary resistance (27). The only two prospective randomized trials done to investigate the effect of early versus delay surgery have not answered

the question whether delayed repair is better for infants with CDH, although; higher survivals have been obtained with delayed surgery (11,12). In our population, delaying surgery favored survival, specifically better survival outcomes were seen when surgery was undertaken after the first 24 hours of life. We believe that this would be an important criteria for infants with CDH to augment their chances of survival.

We conclude that in our hispanic population: 1) contra lateral pneumothorax contributes to a higher mortality; 2) $AaDO_2$ represented a better prognostic indicator than ABG, VI, or OI, and 3) delaying surgical repair was associated with better survival of patients. We believe that adoption of ventilatory strategies aim to decrease barotrauma may further contribute to decrease mortality among infants with CDH cared at our institution.

Resumen

La hernia diafragmática congénita está asociada a una alta mortalidad. El propósito de este estudio fue determinar factores asociados a mortalidad. Se estudió una población de 36 pacientes admitidos al Hospital Pediátrico Universitario durante un periódo de 10 años. Se analizó la data demográfica, data prenatal, complicaciones, parámetros ventilatorios, gases arteriales y data quirurgica. Se comparó el índice ventilatorio, el índice de oxigenación y la diferencia de oxigeno arterial alveolar durante las primeras 24 horas y después de cirugía en los pacientes operados. Se comparó la edad de operación y frecuencia de neumotorax entre sobrevivientes y no sobrevivientes. La sobrevivencia total fue de 40% y la de los infantes operados fue de 61%. Los no sobrevivientes tenían una diferencia de oxigenación arterio alveolar significativamente más alta que los sobrevivientes. Sobrevivieron significativamente más pacientes operados después de 24 horas de vida. Un 39 % de todos los infantes desarrollaron neumotorax y de estos murieron 79%. Concluímos que 1) el neumotorax está asociado a una alta mortalidad, 2) la diferencia de oxigeno arterio alveolar fue un indicador del pronóstico, y que, 3) el retrasar la cirugía por 24 horas estuvo asociada a una mayor sobrevivencia.

Acknowledgement

We thank Dr. Francisco Nieves for his valuable assistance in the elaboration of this manuscript and Luis Herrera, medical student, for his help with the mathematical calculations. We also thank Dr.Cynthia Pérez for her assistance with the interpretation of the statistics.

References

1. Wenstrom KD, Weiner CP, Hanson JW. A five-year statewide experience with congenital diaphragmatic hernia. Am J Obstet Gynecol 1991;165:838-842.
2. Steinborn RH, Kriesmer PJ, Green TP, McKay CJ, Payne NR. Congenital diaphragmatic hernia in Minnesota. Arch Pediatr Adolesc 1994;148:626-631.
3. Langham MR, Kays DR, Ledbetter DJ, Frentzen B, Sandford LL, Richards DS. Congenital diaphragmatic hernia: epidemiology and outcome. Clin Perinatol 1996;23:4:671-688.
4. Breaux CW, 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.
5. Bohn D, Tamura M, Perrin D, Barker G, Rabinovitch M. Ventilatory predictors of pulmonary hypoplasia in congenital diaphragmatic hernia, confirmed by morphologic assessment. J Pediatr 1987;111:423-431.
6. Raphaely RC, Downes JJ. Congenital diaphragmatic hernia: prediction of survival. J Pediatr Surg 1973;8:815-823.
7. Srouji MN, Buck B, Downes J. Congenital diaphragmatic hernia: deleterious effects of pulmonary interstitial emphysema and tension extra pulmonary air. J Pediatr Surg 1981;16:1:45-54.
8. Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CHJ. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. J Pediatr Surg 1995;30:406-409.
9. Miguet D, Claris O, Lapillone A, et al. Preoperative stabilization using high-frequency oscillatory ventilation in the management of congenital diaphragmatic hernia. Crit Care Med 1994;22:S77-S82.
10. Wilson JM, Lund DP, Lillehei CW Vacanti JP. Congenital diaphragmatic hernia, a tale of two cities: the Boston experience. J Pediatr Surg 1997;32(3): 401-405.
11. Goh DW, Drake DP, Bereton RJ. Delayed surgery for congenital diaphragmatic hernia. Br J Surg. 1992;79:644-646.
12. Charlton AJ, Bruce J, Davenport M. Timing of surgery in congenital diaphragmatic hernia. Anaesthesia 1991;46:820-823.
13. Nio M, Haase G, Kennaugh J. A prospective randomized trial of delayed versus immediate repair of congenital diaphragmatic hernia. J Pediatr Surg 1991;29:618-621.
14. De La Hunt MN, Madden N, Scott JES, et al. Is delayed surgery really better for congenital for congenital diaphragmatic hernia? A prospective randomized clinical trial. J Pediatr Surg 1996;31:1554-1556.
15. Cartlidge PHT, Mann NP, Kapila L. Preoperative stabilization in congenital diaphragmatic hernia. Arch Dis Child 1986;61:1226-1228.
16. Shanbhogue LKR, Tam PKH, Ninan G. Preoperative stabilization in congenital diaphragmatic hernia. Arch Dis Child 1990;65:1043-1044.
17. Sakai H, Tamura M, Hosokawa Y, Bryan AC, Barker GA, Bohn D. Effects of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. J Pediatr 1987;111:432-438.
18. Moffit S, Schulze KF, Sahni R, Wung JT, Myers MM, Stolar CJH. Preoperative cardiorespiratory trends in infants with congenital diaphragmatic hernia. J Pediatr Surg. 1995;30:4: 604-611.
19. Pranikoff T, Gauger P, Hirschi R. Partial liquid ventilation in newborn patients with congenital diaphragmatic hernia. J Pediatr Surg 1996;31:613-618.
20. Finer N, Etches P, Kamstra, et al. Inhaled nitric oxide in infants referred for extracorporeal membrane oxidation: dose response. J

Pediatr 1994;124:302-308.
21. Finer NN, Tierney AJ, Hallgren R, et al. Neonatal congenital diaphragmatic hernia and extracorporeal membrane oxidation. Can Med Assoc J 146:501-508, 1992.
22. Glick PL, Leach CL, Besner GE, et al. Pathophysiology of congenital diaphragmatic hernia III: Exogenous surfactant therapy for the high- risk neonate wit CDH. J Pediatr Surg 1992; 27:866-869.
23. Bartlett RH, Gazzaniga A, Toomasian J. Extracorporeal membrane oxygenation in neonatal respiratory failure: 100 cases. Ann Surg 1986;204:236-245.
24. Langer JC, Filler RM, Bohn DJ. Timing of surgery for congenital diaphragmatic hemia: is emergency operation necessary? J Pediatr Surg 1988;23:731-734.
25. UK Collaborative ECMO Trial Group. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-82.
26. Azarow K, Messineo RP, Pearl R, Filler R, Baber G, Bohn D. Congenital diaphragmatic hernia, a tale of two cities: the Toronto experience. J Pediatr Surg 1997;32:395-400.
27. Haugen SE, Linker D, Eik-Nes S, Kufass T, et al. Congenital diaphragmatic hernia: determination of optimal time for operation by echocardiographic monitoring of the pulmonary artery pressure. J Pediatr Surg 1991;25:560-562.