

The Mortality of Congenital Diaphragmatic Hernia

Is Total Pulmonary Mass Inadequate, No Matter What?

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Much progress has been made over the past 20 years in neonatal surgery, but the mortality rate in cases of congenital diaphragmatic hernia (CDH) for babies presenting in the early hours of life has remained high. We have reviewed our experience with special reference to 40 autopsied patients. Hypoplastic lungs were seen in all patients. When the ratio of observed combined lung weight to the expected combined lung weight is calculated, the result is 0.33 ± 0.17 when the expected lung weights are calculated from the babies' birth weight; and 0.36 ± 0.17 when the expected lung weights are calculated from the gestational age. In all patients with high ratios, extensive pneumonia was confirmed. Those patients with pneumonia were eliminated from the calculations. We cannot state unequivocally that hypoplasia of both lungs is the cause of death in all patients with CDH. We can affirm that, in our experience, hypoplasia is present and is probably a major factor in the high mortality rate.

MUCH PROGRESS HAS BEEN made over the past 20 years in neonatal surgery with respect to transport, resuscitation, and intensive care. Nevertheless, despite this progress and improvement in the understanding and care of patients with respiratory insufficiency, the mortality of congenital diaphragmatic hernia remains high, and indeed, unchanged. One author (FMG) has previously reviewed the experience of the Hôpital Ste. Justine Pour les Enfants, from 1960 to 1968.¹ During that period, the mortality rate for babies operated upon within the first 24 hours, and without associated anomalies was 38.5%. In a recent review, Bloss, Beardmore, and Aranda found that this has not changed.²

We have been concerned, as have most pediatric surgeons, with the lack of progress in this area of patient care. Some of these neonates pass through a so-called "honeymoon" period, and yet when autopsy studies are reported, it would seem that the total functional pul-

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monary mass available is inadequate. To examine this question, we studied our series with reference to 40 autopsied cases.

Materials and Methods

This report concerns 40 patients who underwent autopsy whose death resulted from congenital diaphragmatic hernia (CDH). The number seen at the Montreal Children's Hospital from 1968–1981 was 90. Seventy-nine patients were operated upon. Eleven were not operated upon but died, either en route, in the referring hospital, shortly after birth, or with multiple anomalies. One patient was still-born. These 11 cases were part of the autopsy material of 40 patients.

Of the 79 patients operated upon, 63 had respiratory distress and underwent surgery within the first 24 hours of life. Four of these died shortly after emergency operations were carried out. There were 26 deaths following surgery, which represents a 44% mortality (26/59) in those operated upon within the first 24 hours of life. Of the total number, this represents a 35% (26/75) mortality rate.

Associated anomalies were common: cardiac-8, trisomy 18-1, ruptured omphalocele with P.D.A. and A.S.D.-1, anencephaly, and omphalocele-1.

Results of the data analysis on the 59 neonates who were operated upon, with some chance of survival, revealed that in the 19 who had some period of vasodilator therapy, there were 11 deaths (57.8%). Of the 40 who did not receive vasodilator drugs, 25 survived—a mortality rate of 37.5%.

Of the 30 patients who died after surgery, (including the four in extremis), twenty three had no improvement

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TABLE 1.

Wt. (gm)	Gestational Age (wk)	Combined Lung wt. (gm) In () Contralateral Lung Wt.	Obs./Exp. (based on wt.) %	Obs./Exp. (based on gest. age) %	Age to Death (hrs.)
1. 2720	38	13	0.26	.24	36
2. 2778	38	93	1.78	1.75	216
3. 3000	41	41	.78	.73	34
4. 3000	36	25	.47	.54	33
5. 3175	38	28	.50	.52	20
6. 3000	38	41	.78	.77	14
7. 1900	31	12	.28	.38	3
8. 2780	38	36	.69	.68	30
9. 2180	38	25 (18)	.55	.47	24
10. 2970	36	15	.28	.33	20
11. 3041	36	14 (11)	.27	.30	1
12. 3400	—	20 (17)	.31	—	12
13. 2800	40	8 (6)	.15	.14	½
14. 4400	41	24 (20)	.34	.43	3
15. 2500	34	29 (17)	.60	.72	48
16. 2500	38	13	.28	.25	18
17. 1600	33	24 (18)	.68	.65	14
18. 3500	40	22 (9)	.34	.39	10
19. 2800	37	10 (8)	.10	.20	2
20. 3000	39	14 (3)	.26	.25	10
21. 1900	—	12 (9)	.27	—	0
22. 3400	39	32 (21)	.50	.58	24
23. 3600	39	13 (11)	.21	.23	3
24. 3600	40	42	.65	.75	326
25. 2630	37	10 (8)	.21	.20	5
26. 3210	41	16	.28	.28	11
27. 4100	42	21 (12)	.31	.37	5
28. 3300	38	24 (18)	.41	.45	36
29. 1360	—	5 (4)	.16	—	6
30. 3000	37	25 (20)	.46	.50	6
31. 3160	36	20 (16)	.37	.43	24
32. 3190	41	19 (14)	.35	.34	22
33. 2100	36	6 (3)	.12	.13	2
34. 3650	40	30 (23)	.47	.53	48
35. 2600	35	18	.36	.42	7
36. 2400	39	5	.10	.09	1
37. 2740	39	61 (48)	1.16	1.10	192
38. 3070	38	21 (16)	.40	.40	48
39. 3210	37	30 (24)	.50	.60	168
40. 3500	42	10	.15	.17	2

in their preoperative blood gas levels. Of these, eight received vasodilator drug therapy. In this series of 40 autopsies, there were only seven cases where the birth weight was below 2500 gm (Table 1).

The ratio of lung weight to body weight was much less than one half in almost all cases except where pneumonia was present. Expected lung weights related to body weight or related to gestational age are taken from Gruenwald and Minh.³ Thus, not only was ipsilateral hypoplasia present, but striking contralateral hypoplasia, since this ratio was less than one half in 29 of 35 patients when no pneumonia was present (83%). The actual contralateral lung weight is given in parentheses in Table 1 for those 25 autopsies where the measure was made separately.

The examination of the data, when compared either to the expected combined lung weight as compared to the weight of the baby or to the gestational age, is seen

to be low (Table 1). When the total Observed/Expected (Obs/Exp) ratio (%) is examined, the mean is 0.43 ± 0.31 for lung wt/body wt ($n = 40$), and 0.45 ± 0.30 for lung wt/gestational age ($n = 37$). This slight discrepancy may be due to the differences in the weight at birth and to the weight at autopsy as stressed by Gruenwald and Minh,³ and also to the inaccuracy in determining gestational age. When the heavy lung weights due to pneumonia are eliminated, (Patient nos. 2, 15, 24, 37, and 39) the ratios are even more striking— 0.33 ± 0.17 for Obs/Exp when calculated from the expected weights based on body weight and 0.36 ± 0.17 when the expected lung weight is obtained from the gestational age. Thus, statistically, these ratios are both significantly below 1. The mean ratio of the lung weight to body weight for the total group was calculated to be 79 as compared to expected ratio of 177.

There were only seven patients who had a true "honey-

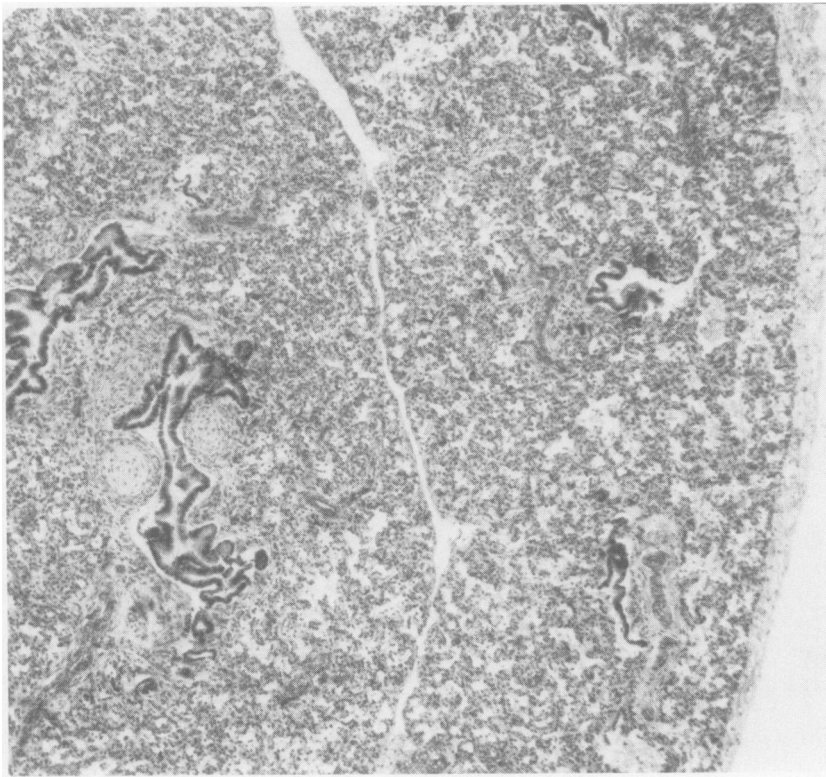


FIG. 1. Low magnification histological appearance of a hypoplastic lung. There is marked proximity of the larger branches of the bronchiolar and vascular tree to the pleural surface, strongly suggesting poor development and expansion of the outer parts of the lobe (HPS $\times 75$).

moon" period; that is, their $p\text{CO}_2$ and $p\text{O}_2$ were acceptable shortly after operation for a period varying from 1–18 hours. The "honeymoon" period has been defined by Bloss, Beardmore, and Aranda as a PaO_2 70 torr on FiO_2 0.6 after surgery followed by deterioration of the patient. Five of the patients died more than 2 days after surgery. In these five patients, marked pneumonia was present, and contributed significantly to lung weight. All of these patients did poorly immediately after surgery (Fig. 1).

Discussion

The difficulty in treating patients having had surgical correction of congenital diaphragmatic hernia is well-known. The mortality has remained unchanged despite progress in transport, resuscitation, and respiratory support. We have been struck by the existence of bilateral lung hypoplasia in the 40 autopsied patients studied. Welch has recently written that true bilateral lung hypoplasia was documented in only 3 of 200 patients.⁴ He states that the term is "overused and underdocumented."⁴ This is not true in our analysis. Nevertheless, it is difficult to understand why some babies do well for a certain period of time and then deteriorate, if their lungs are inadequate initially. This only occurred in seven of our patients. In 29 of 35 patients (eliminating the pneumonia patients) marked contralateral hypoplasia was present.

It is difficult to determine normal lung weights for body weight and gestational age. Gruenwald and Minh have analyzed these difficulties and have presented baseline data on a large number of babies in terms of birth weight, body length, and gestational age related to organ weights.³ They stress that previous studies do not give adequate details to establish the range of a normal standard. They only give expected combined lung weights in their study.

Campanale and Rowland first noted the discrepancy in the surgical and pathological literature in that pathologists found bilateral hypoplasia much more frequently than surgeons.⁵ They suggest that this discrepancy may be due in part to the early death in those patients with lung hypoplasia. Welch's experience is consistent with that of Gross, who is reported (in Campanale and Rowland's paper) not recalling a single instance of hypoplasia.

It is of interest that Gross's good results reported 30 years ago must be, in part, attributed to the selection of patients; the youngest patient operated on was 22 hours of age.⁶

In 1962, Butler and Claireaux reported the experience of the British Perinatal Mortality Survey.⁷ In babies dying of CDH, without other major anomalies and within 24 hours of birth, they found the mean weight of the ipsi-

lateral lung to be 3.7 gm and that of the contralateral lung to be 13.3 gm.

The hypoplasia of the lung in CDH was studied by Kitagawa et al.⁸ By quantitative analysis, they found that the impairment of growth for each structure is not necessarily the same and it differs in each lung. Airway and alveolar numbers are both greatly reduced. Using similar techniques, Hislop and Reid found that the degree of hypoplasia in the ipsilateral and contralateral lungs was different at birth and this difference was maintained until death in a 2½-month-old baby following correction of CDH.⁹ In both of these studies, a presumed increase in the muscularity of the pulmonary vessels was seen. Johnson et al. in 1967 noted that the mortality rate in CDH was highest in babies presenting early and with associated anomalies.¹⁰ In their autopsied patients, the contralateral low lung weight was confirmed again.

Adelman and Benson¹¹ found 18/25 patients at autopsy had pulmonary hypoplasia; the combined lung weight being less than 50% of the predicted.

Mishalany et al. showed that, when the 1966–1976 period was compared to the 1953–1963 period, the mortality was the same, despite earlier operations.¹² They also found that hypoplasia and major cardiovascular anomalies contributed to death. Of 17 patients at autopsy, 12 had severe hypoplasia, four slight to moderate, and only one had normal lung weights. Many of these patients had other severe anomalies.

When examining infants with CDH and associated anomalies, Reale and Esterly showed that radial alveolar counts of the distal airway were significantly decreased, as well as the lung wt/body wt ratios.¹³ They also suggested that decreased proximal branching is a component of pulmonary hypoplasia, because in the majority of infants the decrease in lung weight was greater than could be explained by the decrease in the number of peripheral air spaces. Changes in histologic appearance correlated to the severity of the hypoplasia and were independent of associated anomalies.

Chatrath et al. have shown by ventilatory assessment, in 14 children 6–12 years after CDH repair, that there is a residual defect in ventilatory function despite a normal x-ray appearance.¹⁴ Dunnill has demonstrated that the number of alveoli increases more than tenfold from birth until adulthood, but this occurs mainly during the first 8 years of life.¹⁵ Therefore, the lung buds are in the early stages of branching at the time they are compressed by herniated abdominal contents.

The importance of monitoring blood gases both for prediction of survival and for treatment has been emphasized by many authors in the past 10 years.^{16–19} Raphaely and Downes analyzed their experience correlating

the outcome with the prereduction AaDO₂ and the post-reduction AaDO₂. When prereduction AaDO₂ is greater than 500 torr, the infants ultimately die. They were unable, however, to correlate lung weight ratios with acid-base or blood gas parameters. Bloss and Beardmore have recently reviewed the use of pharmacological support.² It is emphasized that, by selecting the patient with an extremely poor prognosis, extraordinary measures may be attempted, such as extra corporeal oxygenation (ECMO). Several groups have followed Bartlett's lead in the use of ECMO in desperate conditions.²⁰ When combining the results of several studies, ECMO used for a variety of reasons gave 39/68 survivors (57%).^{20–22} When ECMO was used for persistent fetal circulation following CDH repair, the results are 7/10 survivors in patients where, by all historical knowledge, death would have occurred.

Another approach suggested by the innovative research of deLormier is the role of fetal surgery.²³ Intrauterine diagnosis of CDH is now commonplace. It is, of course, difficult to know what the risk of fetal surgery will be in relation to the risk of postnatal repair of CDH. Nevertheless, deLormier has shown that intrauterine repair of CDH will result in lung growth and that, without such repair, hypoplasia of the lungs does result.

We have not settled the controversy regarding the importance of hypoplasia vs. some intrinsic muscular defect in the pulmonary arterial system, which is extremely sensitive to H⁺ ion concentration and to hypoxia. We have established that lung hypoplasia is certainly a major factor in patients doing poorly.

It is probable that the cause of the continuing unchanging mortality rate in patients operated upon for the correction of CDH will be a combination of factors, one of which will certainly be bilateral lung hypoplasia.

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