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Pneumothoraces As a Fatal Complication of Congenital Diaphragmatic Hernia in the Era of Gentle Ventilation

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Abstract

Introduction Pneumothorax remains a life-threatening complication that occurs in congenital diaphragmatic hernia (CDH), even under respiratory management with gentle ventilation. The aim of this study was to evaluate the prevalence of pneumothoraces as a fatal complication during the management of CDH based on the results of a nationwide Japanese survey conducted in the era of gentle ventilation.

Materials and Methods A retrospective cohort study was performed as part of a nationwide Japanese survey of CDH. A total of 510 neonates with isolated CDH born between 2006 and 2010 were included in this study. The patients were divided into four groups according to operative findings related to the diaphragmatic defect size and operability, which represents the disease severity: defects less than 25%, defects more than 25% but less than 75%, defects more than 75%, and a patient group that was unable to undergo surgery. The prevalence of pneumothorax and the survival rate were compared with respect to each disease severity group. Each case was evaluated to determine whether the development of a pneumothorax was the primary cause of death.

Results Of the 510 neonates with isolated CDH, 69 patients developed a pneumothorax before and/or after surgical intervention. Of the 69 patients 38 patients died, and only 26 patients were discharged from the hospital without any major morbidity that requires home treatment ("intact discharge"). The prevalence of pneumothorax increased and the survival rate and intact discharge rate decreased as the severity of the disease worsened. The number of patients whose pneumothorax was presumed to

Keywords
- congenital diaphragmatic hernia
- pneumothorax
- gentle ventilation
- lung injury
- pulmonary hypoplasia

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be the primary cause of death also increased as the severity of the disease worsened. The survival rate of the patients with pneumothorax was significantly lower than that of the patients without pneumothorax among the groups with 25 to 75% defects and 75% or more defects.

Conclusions Pneumothoraces was found to more likely occur in neonates with CDH associated with a large defect of the diaphragm. The survival rate and intact discharge rate decreased as the severity of the disease worsened, especially among the patients who developed pneumothorax accompanied by large diaphragmatic defects. No other risk factors related to pneumothorax occurrence were found, except for the severity of the disease itself, thus suggesting that pneumothorax was associated with a lethal outcome in neonates with CDH associated with a large defect of the diaphragm.

Introduction

Congenital diaphragmatic hernia (CDH) remains one of the most challenging neonatal diseases facing neonatologists and pediatric surgeons, as it continues to be associated with a high mortality and morbidity due to pulmonary hypertension and pulmonary hypoplasia. Over the past several decades, there have been advances in treatment strategies including extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and fetal interventions that have improved the outcomes of CDH patients. However, CDH patients exhibit a broad range of disease severity depending on the components of pulmonary hypertension and pulmonary hypoplasia, which directly affects mortality and morbidity.

Accumulating evidence has shown that ventilator-induced lung injury caused by hyperventilation can have a significant negative impact on short-term outcomes[1,2] and long-term pulmonary sequelae[3,4] in neonates with CDH. To prevent the negative effects of hyperventilation, "gentle ventilation" strategies based on the concept of permissive hypercapnia and permissive hypoxia have been adopted as standard protocol for the treatment of neonatal CDH in many institutions.[5–9] However, even under treatment with a gentle ventilation strategy, the incidence of pneumothorax occurrence, a life-threatening preoperative and/or postoperative complication, reportedly remains high, with rates ranging from 18 to 36%.[10–13] The aim of this study was to evaluate the prevalence of pneumothorax as a fatal complication during the management of CDH and to analyze factors contributing to the development of pneumothoraces based on the results of a nationwide Japanese survey conducted in the era of gentle ventilation strategies.

Materials and Methods

Patient Selection

This retrospective cohort study was performed as part of a nationwide survey of neonatal CDH conducted in 2011 with the support of the Ministry of Health, Labor and Welfare of Japan.[14] The study was performed after being approved by the ethics committee of Osaka University Hospital (approval number of 11017) and the independent ethics committees of five other participating institutions: Hyogo College of Medicine, National Center for Child Health and Development, Kyushu University, Nagoya University Hospital, and Osaka Medical Center and Research Institute for Maternal and Child Health. Data obtained from 72 institutions that consented to participate in a questionnaire survey targeted to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals were retrospectively evaluated. Data were collected as case report forms requesting further details about the patients by the data center that was located in Osaka University Graduate School of Medicine. The entered data were cross-checked twice by the data center and then were fixed after data cleansing. A total of 614 neonates with CDH were born between 2006 and 2010; the overall profiles of the patients are described elsewhere.[14] This study was conducted using only the data of 520 isolated CDH cases defined as CDH infants who did not have serious congenital anomalies, such as major cardiac anomalies or unfavorable chromosomal abnormalities. Four patients with no description of the development of a pneumothorax and six patients whose diaphragmatic defect size was not rated by a surgeon were excluded from this study. Therefore, 510 patients with isolated neonatal CDH were ultimately included in the following analysis.

Data Collection

The primary outcome measure was the occurrence of pneumothorax independent of surgical repair of the diaphragm. We defined pneumothorax as an air leakage from the lungs which was diagnosed by chest X-rays. The cases of preoperative and/or postoperative pneumothorax and of ipsilateral, contralateral, and bilateral pneumothoraces were all included in the primary outcome measures. The secondary outcome measures were survival to discharge, defined as surviving until the time of discharge from the hospital, and "intact discharge," which is a new concept for prognostic evaluation, defined as being discharged from the hospital without any major morbidity that requires home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, parenteral nutrition, or vasodilator administration.[15] The patient demographics, including gestational age,

birth weight, Apgar score at 1 minute, prenatal diagnosis with findings of liver herniation, and lung-to-thorax transverse area ratio,[16] mode of delivery, gender, and side of hernia, were reviewed. Whether a surgery could be performed, the incidence of right-to-left shunting at the ductus within 24 hours after birth and the use of HFOV, iNO, or ECMO were also reviewed. As arterial blood gas data, the highest Pao_2 within 24 hours after birth, including the ventilator settings and the lowest $Paco_2$ within 24 hours after birth were analyzed. Although the blood gas data were in principle obtained from the preductal artery, data for the postductal artery were substituted in patients whose preductal arterial data were not available.

Stratification According to Disease Severity

Among the patients who underwent surgical intervention for a diaphragmatic hernia, the time of surgery after birth, diaphragmatic defect size, and operative method were reviewed. The diaphragmatic defect size was rated by a surgeon to evaluate and classify the severity of disease based on the three levels. The patients were divided into four groups according to operative findings related to the diaphragmatic defect size and operability: defects less than 25%, defects more than 25% but less than 75%, defects more than 75%, and a patient group that was unable to undergo surgery. The prevalence of pneumothorax was compared between the disease severity groups. Each case was evaluated to determine whether the development of pneumothorax was the primary cause of death using a questionnaire. In each subgroup having the same severity of disease, several parameters related to pneumothorax occurrence were compared between the patients who developed pneumothorax and those who did not.

Statistical Analysis

The statistical analyses were performed using the JMP software program (version 9.02; SAS Institute, Inc, Cary, North Carolina, United States). The mean and standard deviation or median and interquartile range were used to describe continuous variables. The frequency and percentages were used to describe categorical data. Student *t*-test and an analysis of variance were used to compare continuous variables. The χ^2 test and Fisher exact test were used to analyze categorical data. *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Prevalence of Pneumothorax and the Survival Rate

An outline of the patient demographics is shown in ►Table 1. Of the 510 neonates with isolated CDH, 361 (70.8%) neonates were diagnosed prenatally and 471 (92.4%) neonates underwent surgical repair for diaphragmatic hernia at a median age of 56 hours after birth. A total of 429 patients (84.1%) survived until discharge, 380 (74.5%) patients of whom were discharged from the hospital without any major morbidity that requires home treatment. (►Table 1).

Table 1 Patient demographics

Patient number	510
Gestational age (d), mean ± SD	265.4 ± 13.8
Birth weight (g), mean ± SD	2,645 ± 452
Apgar score at 1 min, median (interquartile range)	5 (3–7.3)
Prenatal diagnosis, (%)	361 (70.8)
Liver-up, (%)	86/339 (25.4)
L/T ratio < 0.08 (equivalent of o/e LHR < 25%), (%)	57/200 (28.5)
Caesarean section at delivery, (%)	309 (60.6)
Gender (male), (%)	287 (56.3%)
Side of hernia (left/right/both)	463/44/3
Surgery performed for diaphragmatic hernia, (%)	471 (92.4)
Time at surgery after birth (h), median (interquartile range)	56 (28–96)
Patch closure, (%)	118/471 (25.1)
Use of HFOV, (%)	367 (78.9)
Use of iNO, (%)	282 (55.4)
Use of ECMO, (%)	37 (7.3)
Survival to discharge, (%)	429 (84.1)
Intact discharge, (%)	380 (74.5)

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; o/e LHR, observed-to-expected lung area-to-head circumference ratio; SD, standard deviation.

Of the 510 neonates with isolated CDH, 69 (13.5%) neonates developed a pneumothorax before and/or after surgical intervention. Of the 69 patients, 38 (55.1%) patients died and only 26 (37.7%) patients were discharged from the hospital without any major morbidity that requires home treatment. The prevalence of pneumothorax increased as the severity of disease, represented by the operative findings, worsened. Indeed, the prevalence of pneumothorax in the inoperable group was 46%, whereas that observed in the less than 25% defects group was only 2%. The number of patients whose pneumothorax was presumed to be the primary cause of death increased as the severity of the disease increased. Approximately 40% of the patients died of pneumothorax in both the 75% or more defects group and the inoperable group (►Table 2). The survival to discharge rate and intact discharge rate decreased in association with the size of the diaphragmatic defects, and all patients in the inoperable group died. The survival rate was significantly lower in the patients who developed pneumothorax compared with that observed in the patients who did not develop a pneumothorax among the patients with 25 to 75% defects. In the 75% or more defects group, the survival-to-discharge rate as well as the intact discharge rate was significantly decreased among the patients who developed pneumothorax (►Table 2).

Table 2 Incidence and outcomes of pneumothorax occurrence according to the disease severity evaluated based on the operative findings

	< 25% defects	25–75% defects	≥ 75% defects	Inoperable cases	*p*
Patient number, *n*	87	259	125	39	
Pneumothorax, *n* (%)	2 (2)	23 (9)	26 (21)	18 (46)	< 0.001
Pneumothorax as primary cause of death, *n* (%)	0 (0)	2 (9)	10 (38)	8 (44)	0.035
Survival to discharge, *n* (%)	87 (100)	251 (97)	91 (73)	0 (0)	< 0.001
Survival without pneumothorax, *n* (%)	85 (100)	232 (98)[a]	81 (82)[a]	0 (0)	< 0.001
Survival with pneumothorax, *n* (%)	2 (100)	19 (83)[a]	10 (38)[a]	0 (0)	< 0.001
Intact discharge, *n* (%)	87 (100)	228 (88)	67 (54)	0 (0)	< 0.001
Intact discharge without pneumothorax, *n* (%)	85 (100)	210 (89)	61 (62)[a]	0 (0)	< 0.001
Intact discharge with pneumothorax, *n* (%)	2 (100)	18 (78)	6 (23)[a]	0 (0)	< 0.001

[a]$p < 0.01$, with pneumothorax versus without pneumothorax.

Analysis of Risk Factors for the Development of Pneumothorax

In the 25 to 75% defects group, the best oxygenation index within 24 hours after birth was higher and a higher mean airway pressure was required in the patients who developed a pneumothorax compared with that observed in the patients who did not. This may be related to the higher incidence of persistent pulmonary hypertension of the neonate (PPHN), determined based on the incidence of right-to-left shunting at the ductus, in the patients with pneumothorax compared with that observed in patients without pneumothorax. The higher incidence of PPHN resulted in higher rates of iNO and ECMO use in the patients with a pneumothorax compared with those observed in the patients without a pneumothorax (►Table 3).

Patients in the 75% or more defect group showed a higher best oxygenation index and a higher rate of patch closure compared with the patients in the 25 to 75% defects group regardless of pneumothorax occurrence (►Table 3 and ►Table 4). In the 75% or more defects group, there were no significant differences in the parameters, except for a slight difference in the rate of iNO use between the patients who developed pneumothorax and the patients who did not (►Table 4). Inoperable patients clearly showed a lower highest Pao_2, a higher lowest $Paco_2$, and a higher best oxygenation index, thus suggesting a more severe condition of the disease, compared with the patients in the 75% or more defect group without reference to pneumothorax occurrence (►Table 4 and ►Table 5). No significant differences were observed in any parameter between the patients with a pneumothorax and the patients without pneumothorax among the inoperable patients. These patients died at a median age of 2 days after birth regardless of pneumothorax occurrence (►Table 5).

Discussion

Before the mid-1990s, the use of hyperventilation to induce alkalosis was the mainstay of respiratory management for the treatment of PPHN in neonates with CDH, as it was believed that alkalosis could reverse or eliminate ductal shunting by decreasing pulmonary vascular resistance and pulmonary artery pressure.[17] However, subsequent evidence demonstrated that ventilator-induced lung injury caused by hyperventilation could have a significant impact on the survival statistics,[1,2] as well as the long-term pulmonary function, in infants with CDH.[3,4] A large single-center retrospective series of nonsurvivors with CDH treated with a hyperventilation strategy showed that 62 of 68 cases (91%) exhibited evidence of diffuse alveolar damage with hyaline membrane formation, 44 of 62 cases (65%) exhibited evidence of pneumothorax, and 35 of 68 (51%) cases exhibited evidence of parenchymal hemorrhage. Sakurai et al suggested that a significant degree of lung injury was related to a high peak inspiratory pressure and that ventilator-induced lung injury plays an important role in the mortality of patients with CDH.[2]

A permissive hypercapnia strategy was advocated for ventilation in infants with PPHN more than 25 years ago.[18] To prevent the negative effect of hyperventilation in the respiratory management of CDH, a permissive hypercapnia strategy was adopted for neonates with CDH at several institutions in the late 1990s. Case series of CDH have shown that airway pressure limitation and tolerance of hypercapnia, with a focus on preductal oxygen saturation, are the most important factors favorably influencing outcomes.[5–9] The widespread use of iNO therapy from the mid-1990s, which had a selective effect on decreasing pulmonary vascular resistance and pulmonary artery pressure, may have contributed to the switch from hyperventilation strategies to gentle ventilation strategies. Therefore, gentle ventilation strategies based on the concept of permissive hypercapnia and permissive hypoxia have become the mainstay of respiratory management for neonates with CDH. Although the survival rate has improved under the use of gentle ventilation strategies, the incidence of pneumothorax occurrence, a life-threatening preoperative and/or postoperative complication, reportedly

Table 3 Comparison of the parameters in the patients with 25–75% defects in the diaphragm

Development of pneumothorax	No ($n = 236$)	Yes ($n = 23$)	p
Gestational age (d), mean ± SD	267 ± 11	265 ± 9	0.521
Birth weight (g) , mean ± SD	2,804 ± 404	2,757 ± 399	0.589
Apgar score at 1 min, median (interquartile range)	6 (3–8)	4 (3–6)	0.054
Caesarean section at delivery, *n* (%)	141 (60)	16 (70)	0.503
Prenatal diagnosis, *n* (%)	162 (69)	20 (87)	0.093
Liver-up, *n*/*N* (%)	15/149 (10)	2/20 (10)	1.000
L/T ratio < 0.08, *n*/*N* (%)	15/85 (18)	3/11 (27)	0.427
Use of HFOV, *n*/*N* (%)	156/215 (73)	22/23 (96)	0.053
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	235 ± 142	194 ± 122	0.183
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	35 ± 23	38 ± 16	0.548
Best oxygenation index within 24 h after birth, mean ± SD	5.5 ± 5.4	8.4 ± 7.6	0.022[a]
Mean airway pressure (cmH_2O), mean ± SD	12.6 ± 2.9	14.2 ± 2.6	0.015[a]
Right-to-left shunting at ductus within 24 h after birth, *n*/*N* (%)	62/216 (29)	15/23 (65)	0.001[b]
Use of iNO, *n*/*N* (%)	107/235 (46)	18/23 (78)	0.004[b]
Use of ECMO, *n*/*N* (%)	5/236 (2)	3/23 (13)	0.026[a]
Time of surgery after birth (h), median (interquartile range)	52 (28–85)	76 (39–141)	0.293
Patch closure, *n*/*N* (%)	26/236 (11)	4/23 (17)	0.319

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide L/T ratio, lung-to-thorax transverse area ratio.
[a]$p < 0.05$.
[b]$p < 0.01$.

Table 4 Comparison of the parameters in the patients with ≥ 75% defects in the diaphragm

Development of pneumothorax	No ($n = 99$)	Yes ($n = 26$)	p
Gestational age (d), mean ± SD	262 ± 14	263 ± 14	0.828
Birth weight (g), mean ± SD	2625 ± 463	2779 ± 453	0.131
Apgar score at 1 min, median (interquartile range)	3 (2–5)	3 (2–4)	0.493
Caesarean section at delivery, *n*/*N* (%)	66 (67)	18 (69)	1.000
Prenatal diagnosis, *n*/*N* (%)	83 (84)	23 (88)	0.762
Liver-up, *n*/*N* (%)	38/77 (49)	9/23 (39)	0.478
L/T ratio < 0.08, *n*/*N* (%)	20/44 (45)	8/16 (50)	0.778
Use of HFOV, *n*/*N* (%)	82/95 (86)	24/26 (92)	0.521
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	184 ± 128	195 ± 146	0.698
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	38 ± 18	36 ± 11	0.700
Best oxygenation index within 24 h after birth, mean ± SD	12.8 ± 13.3	15.6 ± 16.9	0.411
Mean airway pressure (cm H_2O), mean ± SD	14.3 ± 3.5	14.1 ± 2.6	0.834
Right-to-left shunting at ductus within 24 h after birth, *n*/*N* (%)	53/92 (58)	19/25 (76)	0.109
Use of iNO, *n*/*N* (%)	78/99 (79)	25/26 (96)	0.043[a]
Use of ECMO, *n*/*N* (%)	15/99 (15)	5/26 (19)	0.563
Time of surgery after birth (h), median (interquartile range)	69 (28–123)	100 (26–129)	0.893
Patch closure, *n*/*N* (%)	67/98 (68)	19/26 (73)	0.847

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; SD, standard deviation
[a]$p < 0.05$.

Table 5 Comparison of the parameters in the patients who were unable to be treated with surgical intervention

Development of pneumothorax	No ($n = 21$)	Yes ($n = 18$)	p
Gestational age (d), mean ± SD	263 ± 18	260 ± 27	0.681
Birth weight (g), mean ± SD	2,645 ± 577	2,633 ± 690	0.952
Apgar score at 1 min, median (interquartile range)	2 (1–5)	2 (1–4)	0.871
Caesarean section at delivery, *n* (%)	12 (57)	11 (61)	1.000
Prenatal diagnosis, *n* (%)	17 (81)	12 (67)	0.465
Liver-up, *n*/*N* (%)	13/16 (81)	7/11 (64)	0.391
L/T ratio < 0.08, *n*/*N* (%)	6/11 (55)	3/5 (60)	1.000
Use of HFOV, *n*/*N* (%)	19/19 (100)	12/12 (100)	NA
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	54 ± 43	44 ± 14	0.433
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	51 ± 18	61 ± 38	0.328
Best oxygenation index within 24 h after birth, mean ± SD	56 ± 46	38 ± 9	0.266
Mean airway pressure (cm H_2O), mean ± SD	17.8 ± 4.4	16.1 ± 2.4	0.290
Right-to-left shunting at ductus within 24 h after birth, *n*/*N* (%)	16/19 (84)	9/11 (82)	0.866
Use of iNO, *n*/*N* (%)	18/21 (86)	11/18 (61)	0.141
Use of ECMO, *n*/*N* (%)	3/21 (14)	5/18 (28)	0.432
Survival time (d), median (interquartile range)	2 (2–5.5)	2 (2–5.8)	0.920

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; SD, standard deviation.

remains high,[11,13] even when HFOV, which is thought to be a protective method for minimizing ventilator-induced lung injury, is initially applied.[10,12] Moreover, Boloker et al and Migliazza et al have reported that the mortality rate considerably increases once a pneumothorax develops.[11,12]

Therefore, we analyzed the prevalence of pneumothorax based on the results of a nationwide Japanese survey of neonatal CDH. According to the questionnaire survey concerning the management strategy of each institution, which was conducted simultaneously with this survey and is described in detail elsewhere,[19] a gentle ventilation strategy was adopted in 87% of the institutions, and more than 80% of the institutions preferred to use HFOV initially or proactively. Although the tolerable levels of preductal $Paco_2$ and Pao_2 varied widely, almost all of the Japanese institutions treated CDH patients based on the concept of permissive hypercapnia and permissive hypoxia. Of the 510 isolated CDH neonates, 69 (13.5%) neonates developed a pneumothorax preoperatively and/or postoperatively, more than half of whom died, even under a gentle ventilation strategy.

We stratified the patients according to the disease severity represented by the diaphragmatic defect size, as the mortality of CDH is reported to be dependent on the defect size of diaphragm.[20,21] Although the inoperable patients could not be classified using the defect size as determined by the operative findings, we assumed that those patients were the most severe cases because they were too severe to be stabilized for surgical intervention. In fact, inoperable patients turned out to be more critical than the patients with 75% or more defects judging according to various parameters. The prevalence of pneumothorax was evidently dependent on the disease severity, as represented by diaphragmatic defect size and operability of the patient. The number of patients whose primary cause of death was a pneumothorax was also dependent on the severity of the disease. The survival to discharge rate and intact discharge rate decreased in association with the severity of the disease, and this trend was more significant in the patients who developed a pneumothorax, especially among those with a more severe condition. As the diaphragmatic defect size and operability status are assumed to express the degree of pulmonary hypoplasia, the high prevalence and mortality of pneumothorax are dependent on the degree of pulmonary hypoplasia.

We therefore attempted to identify other risk factors for the development of a pneumothorax with respect to the underlying condition or respiratory management by comparing several parameters between patients with the same level of disease severity. Among the patients with 25 to 75% defects, the best oxygenation index, mean airway pressure, incidence of right-to-left shunting at the ductus, use of iNO, and ECMO were higher in the patients who developed a pneumothorax. However, these differences were not thought to be the causes of pneumothorax occurrence, rather the underlying conditions representing the severity of the disease. In fact, no other risk factors for the development of pneumothorax were found in the 75% or more defects and inoperable groups. These results suggested that the cause of pneumothorax occurrence was the pulmonary hypoplasia itself, and it is inevitable that pneumothorax occurrence will likely be encountered at a constant rate when treating neonates with CDH associated with severe pulmonary hypoplasia. Namely, mortality was the only difference observed for

the patients in the severe condition with pneumothorax compared with those without pneumothorax. Therefore, clinicians must seek to use "more gentle ventilation" strategies and be prepared at any time to quickly treat sudden respiratory deterioration due to pneumothorax occurrence.

A single-center retrospective study revealed that the only statistically significant predictor of the need for ECMO in infants with left CDH and respiratory failure after 6 hours of iNO therapy is the presence of a pneumothorax requiring chest tube placement.[22] There is a current trend toward the significantly decreased use of ECMO in Japan because of advances in respiratory management,[14] and the incidence of ECMO in this series was only 37 cases (7.3%), with a survival rate of 41%. The more proactive and more rapid application of ECMO, which can allow the lung to rest and is considered to be the "ultimate gentle ventilation," in cases of acute deterioration due to pneumothorax occurrence may be helpful to improve both survival and intact discharge rates.

A major limitation of this study is that it was conducted in a retrospective manner using a questionnaire requesting details about the patients. Many of the institutions had a small number of cases, and the treatment strategies for neonates with CDH were determined according to the clinical decisions of each institution, although most of the institutions advocated a gentle ventilation strategy.[19] Unfortunately, more detailed information regarding pneumothorax occurrence, such as the time of pneumothorax recognition, whether the condition was ipsilateral or contralateral or preoperative or postoperative and whether a chest tube was required, was not included in the questionnaire. Because chest tubes are not currently placed routinely at the time of surgery in most Japanese institutions, a postoperative ipsilateral pneumothorax may also be a problem that can sometimes lead to mortality. More detailed prospective studies are therefore needed to analyze risk factors for the development of pneumothoraces and to establish a comprehensive strategy for treating pneumothorax occurrence in neonates with CDH in the era of gentle ventilation.

Conclusions

Pneumothoraces were found to more likely occur in neonates with CDH associated with a large defect of the diaphragm. The survival rate and intact discharge rate decreased as the severity of the disease worsened, especially among the patients who developed a pneumothorax accompanied by large diaphragmatic defects. No other risk factors related to pneumothorax occurrence were found, except for the severity of the disease itself, thus suggesting that pneumothorax was associated with a lethal outcome in neonates with CDH associated with a large defect of the diaphragm. It is necessary to establish a comprehensive strategy for treating pneumothorax occurrence in neonates with CDH in the era of gentle ventilation.

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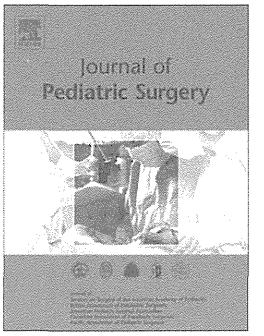

The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias

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Original article

The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias

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Abstract

Background/Purpose: The purpose of this study was to clarify the relationship between the lung to thorax transverse area ratio (L/T ratio) and the observed to expected lung area to head circumference ratio (O/E LHR), based on the results of a nationwide Japanese survey conducted in 2011, and to evaluate the compatibility of these prognostic predictors of fetal CDH.

Methods: Two hundred and forty-two prenatally diagnosed isolated CDH patients born between 2006 and 2010 were included in the present analysis. A regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on 191 simultaneous measurements of these parameters in 120 patients.

Results: The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233+ (0.00222 x O/E LHR), ($R=0.847$, $p<0.0001$). According to this equation, 25% of the O/E LHR, the cut-off value used in the fetal intervention for CDH, was equivalent to a L/T ratio of 0.08, a commonly accepted cut-off value for identifying the most severe cases of fetal CDH.

Conclusions: As there is a positive correlation between the L/T ratio and the O/E LHR, these two parameters proved to be used interchangeably according to the linear regression equation.

Keywords: Congenital Diaphragmatic Hernia; prenatal diagnosis; pulmonary hypoplasia; predictive parameter; prognostic factor

Introduction

The mortality and morbidity of infants with congenital diaphragmatic hernia (CDH) mainly depends on the severity of pulmonary hypoplasia. Therefore, an accurate prenatal assessment of pulmonary hypoplasia is necessary to establish an optimal treatment strategy for individuals before birth. Although many prenatal prognostic parameters have previously been proposed by various investigators [1-4], measurement of the residual lung size seems to be one of the most reasonable and realistic methods [5-8].

The lung area to head circumference ratio (LHR) was the most commonly used predictor for CDH in the past [5, 9, 10]. The observed to expected (O/E) LHR has become a standard parameter used for determining the indications for fetal intervention to treat severe cases of CDH [11]. Of note, the O/E LHR was used in the Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial of left CDH patients with severe pulmonary hypoplasia [12, 13]. On the other hand, the lung to thorax transverse area ratio (L/T ratio), which was proposed before the publication of the LHR [5, 6, 9], has been widely used in Japan for the assessment of pulmonary hypoplasia in fetal CDH patients. [6,14-16]. The LHR is no longer considered to be independently predictive of survival [17, 18], as it was shown to increase according to the gestational age [11, 19-21]. In contrast, the O/E LHR is not influenced by gestational age [22] as is the case with the L/T ratio [6, 14, 19], because it is standardized by the normal mean value of the LHR corresponding to the specific gestational age [11]. Both of the indicators are similarly based on the measurement of the contralateral lung area by using tracing methods [6, 21, 23] at the transverse section containing the four-chamber view of the heart.

The relationship between the L/T ratio and the O/E LHR has not been studied, despite their similarities. The purpose of this study was to clarify the relationship between the L/T ratio and the O/E LHR and to evaluate the compatibility of these parameters as prognostic predictors of fetal CDH based on the results of a nationwide Japanese survey.

Materials and methods

Study population

This retrospective cohort study was performed as part of a nationwide Japanese survey of neonatal CDH conducted in 2011. This study was conducted after being approved by the ethics committee of Osaka University Hospital (approval number 11017) and the independent ethics committees of five other participating institutions: Hyogo College of Medicine, National Center for Child Health and Development, Kyushu University, Nagoya University Hospital and Osaka Medical Center and Research Institute for Maternal and Child Health. The data obtained from 72 institutions that consented to participate in a questionnaire survey targeted to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals were retrospectively evaluated. Data were collected as case report forms requesting further details about the patients by the data center located in Osaka University Graduate School of Medicine. The entered data were crosschecked twice by the data center and then were fixed after data cleansing. A total of 614 neonates with CDH were born between 2006 and 2010; the overall profiles of the patients are described elsewhere [24]. Among those subjects, the present study was

conducted using the data of the 364 isolated CDH cases that were prenatally diagnosed.

Isolated CDH was defined as being present in CDH infants who did not have other serious congenital anomalies, such as major cardiac anomalies or unfavorable chromosomal abnormalities. Three cases of bilateral diaphragmatic hernia were excluded from the study. The contralateral lung area accompanied by the thorax area and/or the head circumference was measured at least one time in 242 out of the 364 cases. The initial and final measurements were reported in the case report form if those parameters were measured more than two times. A total of 242 study subjects (400 measurements), which accounted for 39.4% of all 614 CDH patients treated at 45 institutes, were ultimately included in the present analysis. Among those subjects, the thorax area measurement was reported 339 times for 210 patients and the head circumference measurement was reported 251 times for 154 patients. The contralateral lung area, the thorax area and the head circumference were simultaneously measured 191 times in 120 patients.

Collected data

The primary outcome measure was the survival to discharge, which was defined as surviving at the time of discharge from the hospital. The secondary outcome measure was the "intact discharge", which is a new concept for prognostic evaluation, defined as being discharged from the hospital without any major morbidity that requires home treatment, including ventilatory support, oxygen administration, tracheostomy, tube feeding, parenteral nutrition or vasodilator administration [4]. The patient

demographics, including the gestational age, birth weight, Apgar score at 1 minute, presence of liver and stomach herniation, mode of delivery, gender and side of hernia, were reviewed. Whether a surgery could be performed, the size of the diaphragmatic defect, the surgical procedure performed, the use of high-frequency oscillatory ventilation (HFOV), nitric oxide inhalation (iNO), prostaglandin E_1 or extracorporeal membrane oxygenation (ECMO) were also reviewed. As the indication criteria for surgery were not defined prospectively, the operability of each case was determined according to the clinical decisions of each institution. The highest preductal PaO_2, best oxygenation index and the right to left shunting at the ductus which were determined within 24 hours after birth, were reviewed. The contralateral lung area (in square millimeters) and the thorax area (in square millimeters) were measured by manual tracing of the limit of the lung and thorax at the transverse section containing the four-chamber view of the heart in ultrasonography. The head circumference (in millimeters) was measured in the standard biparietal view of ultrasonography. The L/T ratio was defined as the area of the contralateral lung divided by the area of the thorax [19]. The observed LHR, which was the ratio of the contralateral lung to the head circumference, was divided by the appropriate normal mean for gestational age and multiplied by 100 to derive the O/E LHR and expressed as a percentage [21]. The expected LHRs were determined by the published formulas, which are freely available to all by the official calculator in the Tracheal Occlusion To Accelerate Lung Growth (TOTAL) trial website (access http://www.totaltrial.eu/) [12].

Analysis of the relationship between the L/T ratio and the O/E LHR

A simple regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on the simultaneous measurements in 120 cases. Although the initial and final simultaneous measurements were available in 71 cases, only a single simultaneous measurement was available in 49 cases. We decided to use all simultaneous measurements in order to obtain more accurate relationships between the two parameters. The linear regression equation between the L/T ratio and the O/E LHR was derived from the regression analysis. The L/T ratio values which corresponded to the cut-off values of the O/E LHR used in the TOTAL trial entry criteria were calculated according to the linear regression equation.

Patient outcome according to the prenatal prediction of the disease severity

In the 226 cases of left isolated CDH whose liver herniation was evaluated, the survival to discharge rate was reviewed according to the classification of the disease severity used in the TOTAL trial, which were defined by the combination of the O/E LHR and the presence of liver herniation, as proposed by Deprest et al. [25]. In the cases whose O/E LHR was not measured, the O/E LHR was estimated from the L/T ratio using the linear regression equation. The patient demographics, prenatal and postnatal profiles, including parameters indicating the respiratory status, circulatory status, surgical findings and outcome, were compared among the prenatal risk-stratified classifications defined by the combination of the L/T ratio and the presence of liver herniation, as proposed by Usui et al. [16]. In the cases whose L/T ratio was not measured, the L/T ratio was estimated from the O/E LHR using the linear regression

equation. The values of the O/E LHR and L/T ratio were represented by the initial values of two measurements in principle, and the final values were substituted for the patients whose initial value was not available in the case report form.

Statistical analysis

The statistical analyses were performed using the JMP software program (version 9.02; SAS Institute, Inc, Cary, NC, USA). The frequencies and percentages were used to describe categorical data. The means and standard deviation were used to describe continuous variables. The median and interquartile ranges were used to describe Apgar scores. The chi-square test and Fisher's exact test were used to analyze categorical data. The one-way analysis of variance with Tukey's post-hoc honestly significant difference test was used to compare continuous variables. The Kruskal-Wallis test was used for the comparison of the Apgar scores. The log-rank test and Kaplan-Meier method were used to compare the survival times. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

An outline of the patient demographics is shown in Table 1. Of the 242 neonates with prenatally diagnosed isolated CDH, 177 (73.1%) were delivered by Caesarean section and 224 (92.6%) underwent surgical repair for diaphragmatic hernia at a median age of 56 hours after birth. Surgery could not be performed in 18 cases (7.4%) based on the clinical decisions of each institution. It was therefore assumed

that these cases were extremely unstable and were considered to be in too serious of a condition to undergo a surgical repair. Two hundred patients (82.6%) survived until discharge, 177 (73.1%) of whom were discharged from the hospital without any major morbidity that required home treatment **(Table 1)**.

Table 1

Relationship between the L/T ratio and the O/E LHR

Eighteen of the 120 infants whose L/T ratio and O/E LHR were simultaneously determined died, resulting in an 85.0 % survival rate. We found a strong positive correlation between the L/T ratio and the O/E LHR. The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233 + (0.00222 x O/E LHR), where the regression coefficient was 0.00222, correlation coefficient was 0.847 and coefficient of determination was 0.717 ($p<0.0001$) **(Figure 1)**. According to this equation, 15%, 25%, 35% and 45% of the O/E LHRs, the cut-off values used in the TOTAL trial of left CDH patients, were found to be equivalent to 0.06, 0.08, 0.10 and 0.12 L/T ratios, respectively.

Figure 1

Figure 2, Table 2

Patient outcome according to the prenatal prediction of the disease severity

In the 226 cases of left isolated CDH, the survival to discharge rate was reviewed according to the four-step stratification proposed by Deprest et al. [25]. The survival rate exhibited a trend toward a decrease as the severity of the disease increased. However, the effect of the liver herniation seemed to be stronger in our series compared to those in the series described by Deprest et al. (**Figure 2**). In the prenatal risk-stratified classification [16], there were no significant differences in the patient demographics except

for the side of hernia. There were unsurprisingly significant differences in the rate of liver-up and the L/T ratio based on how the each group was defined (**Table 2**). The highest preductal PaO_2 decreased, and the best oxygenation index increased, as the severity of the disease increased. The right to left shunting at ductus evaluated within 24 hours after birth, which suggest the severity of pulmonary hypertension, differed significantly among the three groups, which resulted in the differences in the numbers of patients who used iNO, prostaglandin E_1 and ECMO. Although surgical repair could not be performed in only two (1.3%) cases in group A, surgery was not possible in six out of 16 (35.3%) cases in group C due to their unstable conditions. There were also significant differences in the proportions of patients with diaphragmatic defects exceeding 75%, as rated by the surgical record, as well as the need for patch repair. There were significant differences in the morbidity and mortality among the three groups. The rate of survival to discharge was 93% and the intact discharge rate was 87% in group A, whereas the corresponding rates were 72% and 58% in group B and 35% and 18% in group C, respectively (**Table 3**). There were also statistically significant differences in the survival curves among the three groups (**Figure 3**).

Figure 3, Table 3

Discussion

Since the mortality and morbidity of neonates with CDH primarily depends on the severity of pulmonary hypoplasia, an accurate prenatal assessment of pulmonary hypoplasia is necessary for making a decision about the optimal treatment. Although many prenatal prognostic parameters have been reported