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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Risk Factors for the Recurrence of the Congenital Diaphragmatic Hernia—Report from the Long-Term Follow-Up Study of Japanese CDH Study Group

Kouji Nagata[1] Noriaki Usui[2] Keita Terui[3] Hajime Takayasu[4] Keiji Goishi[5] Masahiro Hayakawa[6] Yuko Tazuke[7] Akiko Yokoi[8] Hiroomi Okuyama[9] Tomoaki Taguchi[1]

[1] Department of Pediatric Surgery, Kyushu University, Fukuoka, Japan
[2] Department of Pediatric Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
[3] Department of Pediatric Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
[4] Department of Pediatric Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[5] Division of Neonatology, Department of Maternal and Perinatal Medicine, National Center for Child Health and Development, Tokyo, Japan
[6] Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan
[7] Department of Pediatric Surgery, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan
[8] Department of Pediatric Surgery, Kobe Children's Hospital, Kobe, Japan
[9] Department of Pediatric Surgery, Hyogo College of Medicine, Nishinomiya, Japan

Address for correspondence Kouji Nagata, MD, Department of Pediatric Surgery, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (e-mail: koujin@pedsurg.med.kyushu-u.ac.jp).

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Abstract

Aim of the Study Few follow-up studies focused on the recurrence regarding the postoperative course of congenital diaphragmatic hernia (CDH) survivors. The aim of this study was to report on risk factor for CDH patients who had the recurrence during the follow-up.

Materials and Methods A multicenter retrospective survey was conducted on neonates diagnosed to have CDH between January 2006 and December 2010. Follow-up survey was conducted between September 2013 and October 2013 (ethical approval: No. 25–222). Nine institutions agreed to participate in this survey. Out of 228, 182 (79.8%) patients were alive and 180 patients were included in this study. Two patients were excluded because the defect had not repaired at the primary operation. The patients were divided into the recurrence group ($n = 21$) and the nonrecurrence group ($n = 159$). Postnatal and postoperative variables were compared between these two groups. Baseline variables which showed significance in univariate analysis were entered into multiple logistic regression analysis for analyzing the recurrence. A value of

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- long-term complication
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$p < 0.05$ was considered to be statistically significant by using the JMP software program (version 9; SAS Institute, Inc, Cary, North Carolina, United States).

Main Results Out of 180, 21 (11.7%) CDH neonates had the recurrence during the course of the follow-up. Five (2.8%) patients had the recurrence before primary discharge and 16 (8.9%) patients had the recurrence after discharge. Univariate analysis showed that liver herniation (crude odds ratio [OR], 7.4; 95% confidence interval [CI], 2.73–23.68), defect size C and D, proposed by the CDH Study Group (crude OR, 7.09; 95% CI, 2.73–19.99) and patch repair (crude OR, 5.00; 95% CI, 1.91–14.70) were risk factors. Multivariate logistic regression analysis showed liver herniation (adjusted OR, 3.96; 95% CI, 1.01–16.92) was the risk factor for the recurrence.

Conclusion A wide spectrum of the disease severity and the rarity of the disease mask the risk of the recurrence for CDH patients. This study showed the only factor to predict the recurrence was the liver herniation. These data will be helpful for providing information for the long-term follow-up of the CDH patients.

Introduction

Recent advances in the prenatal and postnatal congenital diaphragmatic hernia (CDH) treatment strategy, there have been increased improvement in outcome.[1,2] Therefore, much of the clinical interests have shifted to the long-term outcomes of CDH survivors, since as the survivors can suffer from the long-term morbidities, including recurrence, pulmonary disease, gastrointestinal tract disease, hearing loss, impairment in growth and development, and orthopedic deformities.[3]

The reported incidence of recurrent diaphragmatic hernia varies from 5 to 65%.[3–5] The recurrence of the diaphragmatic hernia sometimes causes gastrointestinal tract disorders and respiratory disorders, which will severely affect the quality of life in survivors. Recent articles recommend the chronological follow-up protocol to monitor the recurrence and other complications to be early diagnosed and cured when occurred.[6]

The rarity of CDH makes conducting well-designed clinical studies extremely difficult because no single institution can accrue sufficient patients to reach meaningful conclusions. Therefore, the long-term follow-up study for CDH has based on retrospective studies in a single center experience or from multiple centers using different treatment strategies.[7]

In Japan, the cohort study had started from the multicenter retrospective cohort study for an antenatally diagnosed CDH, and then, performed a nationwide survey to understand the current treatment and the actual outcome during the period from 2006 to 2010.[8] Thereafter in 2013, a long-term follow-up study had performed among the dedicated institutions to better understand the associated long-term complications of CDH survivors. The purpose of this study was to analyze the risk factors for the recurrence among CDH neonates as part of the long-term follow-up study.

Materials and Methods

Patient Selection

This retrospective survey was approved by the ethics committees of the nine representative institutions, including the Graduate School of Medical Sciences, Kyushu University; National Center for Child Health and Development; Nagoya University Hospital; Osaka Medical Center and Research Institute for Maternal and Child Health; Kobe Children's Hospital; Faculty of Medicine, University of Tsukuba; Graduate School of Medical Sciences, Chiba University; Hyogo College of Medicine; and Graduate School of Medicine, Osaka University (representative institutional review board approval no. 25–222, Graduate School of Medical Sciences, Kyushu University).

A nationwide retrospective cohort study was conducted on CDH neonates diagnosed to have CDH between January 2006 and December 2010, and a total of 674 CDH neonates diagnosed during the 5-year period. Subsequent long-term follow-up study was conducted among the Japanese CDH Study Group and finally nine institutions which had 228 CDH neonates in the previous study consented to participate. According to this recurrence survey, 180 patients who had repaired the defect at the primary operation and the survived at least 3 years were included. Two right CDH patients who had not repaired the defect at the primary operation were excluded in this survey. One had to stop the operation because of the decrease in blood pressure during the course of correcting the liver position, while the other had been despaired the operation because of the ipsilateral lung defect.

Data Collection

The postnatal variables, including the presence of a prenatal diagnosis, birth location, sex, the presence of the associated anomalies, the side of the defect, the use of inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO), gestational age at delivery and birth weight, Apgar score at 1 minute, and the lowest oxygenation index (OI)

Table 1 Postnatal characteristics, comparing the Rec and non-Rec

Variables	Rec ($n = 21$)	Non-Rec ($n = 159$)	p value
Prenatal diagnosis (%)	21 (100)	134 (84.3)	0.048
Inborn (%)	21 (100)	134 (86.5)	0.048
Male gender (%)	7 (33.3)	91 (57.2)	0.06
Non–isolated CDH (%)	3 (14.3)	9 (5.7)	0.151
Right side of hernia (%)	2 (9.5)	11 (6.9)	0.651
iNO (%)	20 (95.2)	102 (64.2)	0.001
ECMO (%)	1 (4.8)	9 (5.7)	0.863
Continuous variables			
Gestational age (d), mean ± SD	261.8 ± 18.4	264.8 ± 11.0	0.279
Birth weight (d), mean ± SD	2,533.7 ± 601.5	2,703.3 ± 453.7	0.124
Apgar score at 1 minute, median (interquartile range)	5 (2–7)	5 (3–7)	0.358
Lowest OI, median (interquartile range)	4.8 (3.3–6.4)	3.8 (2.8–5.9)	0.906

Abbreviations: ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; non-Rec, nonrecurrence group; OI, oxygenation index; Rec, recurrence group; SD, standard deviation.

within 24 hours after birth were reviewed. An isolated CDH was defined as the CDH without any associated life-threatening or chromosomal anomalies.[8]

The perioperative variables were also examined. The presence of liver herniation, the type of diaphragmatic closure, and the defect size were also reviewed. Liver herniation was defined as CDH patients whose liver had herniated into the thoracic cavity during the operation. The defect size was determined according to the CDH Study Group's criteria, as previously reported in the literature.[8–10]

Statistical Analysis

The patients were divided into the recurrence group (Rec) ($n = 21$) and nonrecurrence group (Non-Rec) ($n = 159$). Postnatal and intra- or postoperative variables were compared between these two groups. The frequencies and percentages were used to describe the categorical data. The χ^2 test and Fisher exact test were used for the analysis of the categorical data. The mean and standard deviation or median and interquartile range were used to describe continuous variables. Student t-test and an analysis of variance were used to compare continuous variables. Baseline variables which showed significance in univariate analysis were entered into multiple logistic regression analysis for analyzing the recurrence. Kaplan–Meier analysis and Cox proportional hazards regression were also used for the recurrence analyses. The statistical analyses were performed with the JMP software program (version 9; SAS Institute, Inc, Cary, North Carolina, United States). A value of $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient Characteristics and the Comparison between Recurrence Group and Nonrecurrence Group

Out of 228, 182 (79.8%) patients were alive and 180 patients were included in this study. A total of 11.6% ($n = 21/180$) CDH patients had a recurrence during the course of the follow-up. Out of 21, 20 CDH patients had reoperations and 1 patient have not operated during the follow-up period. Five patients had a primary recurrence before the primary discharge. Three patients had a second recurrence and all of them had repaired by using an abdominal muscle flap procedure.

The postnatal characteristics of the CDH neonates are shown in ►Table 1, with comparison between the Rec and Non-Rec. There were significant differences in the prenatal diagnosis rate and the inborn rate (Rec vs. Non-Rec = 100 vs. 84.3%, $p = 0.048$ and 100 vs. 86.5%, $p = 0.048$, respectively). There were no significant differences between two groups, according to the rate of the male gender, nonisolated CDH, right side hernia, and the use of ECMO. The use of ECMO was only 4.8% ($n = 1/21$) in Rec and 5.7% ($n = 9/159$) in Non-Rec. There were no differences in the gestational age, birth weight, Apgar score at 1 minute, and the lowest OI. Other variable which revealed significance was the iNO. These advanced therapies are recognized as the useful instruments for the persistent pulmonary hypertension, although their indications were not standardized in participants.

The perioperative characteristics of the CDH neonates are shown in ►Table 2. A total of 76.2% ($n = 16/21$) had liver herniation in Rec and 30.2% ($n = 48/159$) in Non-Rec. Patch repair was also significantly correlated to the recurrence with 22.1% ($n = 15/21$) in patch repair group, although 5.4% ($n = 6/112$) in direct repair group. Defect size was also correlated to the recurrence with 28.6% ($n = 14/49$) had larger defect (C and D) and 5.3% ($n = 7/131$) had smaller defect (A and B). Liver herniation, patch repair, and the defect size were valuables which were significantly associated with the recurrence. As would be expected, the patients who had a large defect are likely to involve the liver in thoracic cavity and require the patch during the operation. Another significant variable was the age at operation. The severity of disease might affect the timing of operation; however, there also was

Table 2 Preoperative characteristics, comparing the Rec and Non-Rec

Variables	Rec ($n = 21$)	Non-Rec ($n = 159$)	p value
Liver herniation (%)	16 (76.2)	48 (30.2)	0.0001
Patch repair at the primary operation			
Direct repair, $n = 112$ (%)	6 (5.4)	106 (94.6)	0.001
Patch repair, $n = 68$ (%)	15 (22.1)	53 (77.9)	
Defect size			
A and B, $n = 131$ (%)	7 (5.3)	124 (94.7)	< 0.001
C and D, $n = 49$ (%)	14 (28.6)	35 (71.4)	
Continuous variables			
Age at repair (h), median (interquartile range)	101 (54.5–145.5)	50 (24–77)	0.025
Length of stay (d), mean ± SD	86.2 ± 53.7	84.1 ± 123.8	0.939
Follow-up period (d), mean ± SD	1,645.8 ± 538.4	1,682.4 ± 594.5	0.787

Abbreviations: Non-Rec, nonrecurrence group; Rec, recurrence group; SD, standard deviation.

no definite standardization among participants. Also, the technical and material aspects were also excluded because of the absence of the standardized protocol. Actually, nine out of seven institutions, including 139 patients used the PTFE patch (GORE-TEX Soft Tissue Patch; W. L. Gore & Associates, Inc., Arizona, United States), whereas one institution, including 27 patients used polyester patch (Sauvage Filamentous Fabric; C.R. Bard, Inc., New Jersey, United States) and the other institution, including 14 patients used polypropylene and PTFE composix mesh (COMPOSIX EX Mesh; C.R. Bard, Inc.). There were neither significant differences in the length of hospital stay nor the follow-up period between these groups.

Analysis of Risk Factors and Prediction for Recurrence

A multivariate analysis was performed for all baseline variables which were significant in the univariate analysis for recurrence. Baseline variables were considered as the presence of the prenatal diagnosis, inborn, male gender, nonisolated CDH, right side hernia, gestational age, birth weight, Apgar score at 1 minute, the lowest OI, liver herniation, patch repair, defect size, and the length of stay. Other variables were not included in the multivariate analysis because the postnatal treatment strategy was not standardized among the cooperative institutions.

Univariate analysis in ►Table 3 showed that liver herniation (crude odds ratio [OR], 7.4; 95% confidence interval [CI], 2.73–23.68), defect size C and D (crude OR, 7.09; 95% CI, 2.73–19.99), and patch repair (crude OR, 5.00; 95% CI, 1.91–14.70) were significant risk factors. Multivariate logistic regression analysis in ►Table 4 showed liver herniation (adjusted OR, 3.96; 95% CI, 1.01–16.92) was the only significant risk factor for the recurrence. Defect size C and D (adjusted OR, 3.79; 95% CI, 0.86–23.12) and patch repair (adjusted OR, 1.30; 95% CI, 0.24–8.83) had not showed significance. The Kaplan–Meier analysis associated with the recurrence in ►Fig. 1 showed the recurrence rate after 6 months, 1 , and 2 years of the primary operation. The each recurrence rate was higher in liver herniation group, compared with the nonliver herniation group (liver herniation vs. nonliver herniation = 6 months: 15.7 vs. 1.7%, 1 year: 18.9 vs. 4.4%, and 2 years: 25.4 vs. 4.4%). Cox proportional hazards regression analyses showed significance in liver herniation (hazard ratio, 3.66; 95% CI, 1.03–14.42; $p = 0.045$).

Discussion

As the survival rate for patients with CDH have increased during the past decades with the advent of "gentle ventilation" and specific strategy and care, clinicians has led to focus on the frequency and importance of postoperative morbidities.[1,3,6] Significant morbidities such as the recurrence, respiratory diseases, neurocognitive delay, gastrointestinal disorders, hearing loss, poor growth, chest deformity, and the complications associated with congenital anomalies continue

Table 3 Univariate analysis for the recurrence

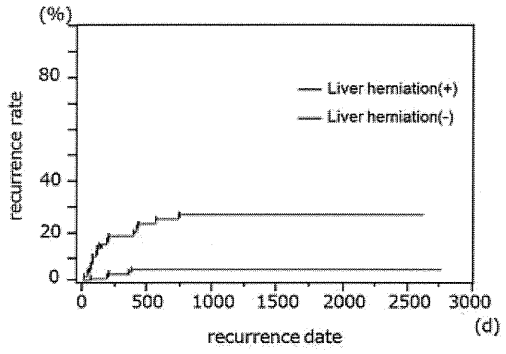
Variables	Crude odds ratio	95% CI	p value
Liver herniation	7.4	2.73–23.68	0.0002
Defect size C and D	7.09	2.73–19.99	< 0.001
Patch repair	5.00	1.91–14.70	0.0017

Abbreviation: CI, confidence interval.

Table 4 Multiple logistic regression analysis for the recurrence

Variables	Adjusted odds ratio	95% CI	p value
Liver herniation	3.96	1.01–16.92	0.0483
Defect size C and D	3.79	0.86–23.12	0.0796
Patch repair	1.30	0.24–8.83	0.7666

Abbreviation: CI, confidence interval.



Recurrence rates	Liver herniation (+) (n=64)	Liver herniation (-) (n=116)
6 months after the operation	15.7%	1.7%
1 year after the operation	18.9%	4.4%
2 years after the operation	25.4%	4.4%

Fig. 1 The Kaplan–Meier analysis for the recurrence ($n = 21$). Cox proportional hazards regression analyses showed significance in liver herniation (hazard ratio, 3.66; 95% confidence interval, 1.03–14.42; $p = 0.045$).

to affect the quality of life of many infants with CDH beyond the neonatal period.[1,3] Recurrence is one of the most insidious complication during the follow-up. Reoperation will be considered when the patients revealed herniation of the stomach or intestinal loops, or progressing elevation of the diaphragm over time. However, few systemic reviews of the CDH patients with recurrence exist, and therefore, risk factors for predicting the recurrence remains controversial.[4–6,11,12] Most of the literatures associated with the recurrence were small case series or the insufficient follow-up period with lack of important data.[4–6,11,12] In this survey, 180 CDH survivors with more than 3-year follow-up period were collected, these numbers and periods might be favorable.

The previously reported risk factors for the recurrence were larger defect, prosthetic patch, surgeon's skills or experiences, ECMO, and minimally invasive surgery (MIS).[4–6,11–13] The risk factors for the recurrence might be composed of two kinds of aspects: one is the severity of the disease, and the other is the technical issue. Likewise, in this study, baseline variables and univariate analysis showed the significant differences in liver herniation, larger defect, and patch repair. These three factors were confounding factors, which will certainly represent the severity of the disease among CDH patients. Finally, multiple logistic regression analysis showed the significance in liver herniation. This result showed the correlation between diaphragmatic defects; otherwise, the disease severity might be strongly associated with the recurrence. In addition, the chronological recurrence rates between liver herniation group and nonliver herniation group were primarily sated as follows: the liver herniation group became plateau to 25.4% at 2 years after the primary operation, and nonliver herniation group become plateau to 4.4% at 1 year after the primary operation. This statistical analysis would be practical and helpful for the parental counseling and the prognostic prediction.

In this study, no one was treated by MIS, 4 were treated via a transthoracic approach, and 176 were treated via a transabdominal approach. The surgical approach for CDH varies regionally and the technical problems might exist, especially, in the field of MIS. Although, a meta-analysis showed a statistically higher recurrence rate in the thoracoscopic group,[13] the actual risk and benefit of MIS might need more time to conclude because the MIS for CDH repair was still not yet to be established at present.

The limitation of this study was the restriction in retrospective multicenter cohort study design. In this study, nine cooperative institutions do not have the standardized protocol, and hence, the indications for treatment were lack of consensus. Therefore, the indication for iNO and the timing of operation were different, in which these factors had to be excluded from the univariate analysis in consideration for bias. Technical and material aspects, such as the cone-shaped Dualmesh (W. L. Gore & Associates, Inc., Arizona, United States) patch, or the PTFE/Marlex composite graft were not also examined; nevertheless, recent literature showed significances in recurrence rate.[4,6] These technical and material factors should be standardized when we plan to perform the prospective study in future.

Two-thirds of CDH patients with recurrence were reported to be asymptomatic at the time of diagnosis.[6] Late diagnosis of recurrence sometimes leads patients to the risk of bowel obstruction, respiratory failure, and the other serious sequelae. Recent CDH follow-up protocol recommends the periodic plain chest X-ray and the other additional complete examinations when the recurrence are to be suspected.[5,6] Ideally, establishing an international, multicenter long-term follow-up registry will be favorable to better understand the incidence patterns of morbidity in CDH patients.

A wide spectrum of the disease severity and the rarity of the disease mask the risk of the recurrence for CDH patients. This study showed the only factor to predict the recurrence was the liver herniation. These data will be helpful for providing information for the long-term follow-up of the CDH patients.

Conflict of Interest
None.

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ORIGINAL ARTICLE

Prognostic factors of gastroesophageal reflux disease in congenital diaphragmatic hernia: a multicenter study

Keita Terui · Tomoaki Taguchi · Keiji Goishi · Masahiro Hayakawa · Yuko Tazuke · Akiko Yokoi · Hajime Takayasu · Hiroomi Okuyama · Hideo Yoshida · Noriaki Usui · The Japanese Congenital Diaphragmatic Hernia Study Group

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Abstract

Purpose Gastroesophageal reflux disease (GERD) is one of the concomitant problems in infants with congenital diaphragmatic hernia (CDH). We assessed risk factors of GERD in CDH patients.

Methods The retrospective observational study for CDH infants was conducted. Cases of CDH who were born between January 2006 and December 2010, were operated in the 9 participating institutions, and survived to discharge were included. Completion of medical therapy for GERD and incidence of surgery were primary outcomes. Kaplan–Meier survival analysis and Cox proportional hazards regression were used.

Results In 182 cases of CDH, the medical therapies for GERD were performed in 23.8 % (40/168), and were completed in 60.0 % (24/40). Prenatal detection of CDH (HR 5.87, CI 1.6–18.8, $p = 0.012$) and tube feeding at discharge (HR 5.04, 95 % CI 1.3–33.1, $p = 0.016$) were significantly correlated with unsuccessful weaning from medical therapy. Surgery for GERD was performed in 10.7 % (18/169). Gestational age (HR 4.78, 95 % CI 1.5–21.1, $p = 0.006$) and diaphragmatic defect of more than 75 % (HR 4.3, 95 % CI 1.6–12.9, $p = 0.005$) were significantly correlated with need for antireflux surgery.

Conclusion Diaphragmatic defect of more than 75 % was risk factor of future need for antireflux surgery.

Keywords Congenital diaphragmatic hernia · Gastroesophageal reflux · Diaphragm · Fundoplication · Long-term care

Introduction

Gastroesophageal reflux disease (GERD) is one of the concomitant problems in infants with congenital

K. Terui (✉) · H. Yoshida
Department of Pediatric Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8677, Japan
e-mail: kta@cc.rim.or.jp

T. Taguchi
Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Kyushu, Japan

K. Goishi
Division of Neonatology, Department of Maternal and Perinatal Medicine, National Center for Child Health and Development, Tokyo, Japan

M. Hayakawa
Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan

Y. Tazuke · N. Usui
Department of Pediatric Surgery, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

A. Yokoi
Department of Pediatric Surgery, Kobe Children's Hospital, Kobe, Japan

H. Takayasu
Department of Pediatric Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

H. Okuyama
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

H. Okuyama
Department of Pediatric Surgery, Hyogo College of Medicine University, Hyogo, Japan

diaphragmatic hernia (CDH). Nearly 40 % of CDH survivors are thought to have symptomatic GERD [1]. Possible etiologies of GERD in CDH include abnormal hiatal anatomy at the gastro-esophageal junction, lack of an angle of His, herniation of the stomach into the chest and dilatation of the esophagus [2]. Treatment options for infantile GERD include lifestyle modifications, pharmacologic agents, and antireflux surgery. Surgical approaches are reserved for children who have intractable symptoms or who are at risk for life-threatening complications of GERD [3]. Historically, the risk of GERD in CDH is thought to have increased with improvement of the survival of severe CDH [4, 5]. Need for patch is one of risk factors of severe GERD which needs interventions [6–9], however, some have reported negative [10] or converse data [11] in pathological GERD. Indicators of severity of CDH, such as liver herniation [7], thoracic position of the stomach [9, 10], and time of diagnosis [10] were another risk factors reported to date. Meanwhile, Kamiyama et al. [11] reported that esophageal acid exposure was not influenced by severity of CDH based on detailed pH monitoring. Furthermore, Peetsold et al. [9] reported it was difficult to predict occurrence of GERD during long follow-up of CDH patients. Also, the natural history of GERD associated with CDH has not been clear yet. Bagolan and Morini reported that overall rate of surgery for GERD in CDH patients was 19 % based on the review of 21 literatures [12]. Abdullah et al. [13] reported 17 % of CDH cases underwent fundoplication according to the US database with a total of 2,173 cases of CDH. On the other hand, some reports have revealed that natural history of GERD associated with CDH has the tendency to resolve without surgery, as well as isolated GERD [9, 13, 14]. Hence, in CDH survivors, GERD cases who need antireflux surgery and the cases with the tendency to resolve without surgery are mixed. To choose appropriate treatments for infantile GERD, we have to know the characteristics of the cases which have no tendency to resolve without surgery. In this study, "the cases who have no tendency to resolve without surgery" was interpreted as "the cases with unsuccessful weaning from medical therapies" and "the cases with eventual need for surgery". By assessing these two factors, the natural history and the risk factors of GERD associated with CDH were discussed in the present study.

Materials and methods

Patient selection

This study was subsequent of a nationwide survey of neonatal CDH conducted by The Japanese Congenital Diaphragmatic Hernia Study Group in 2011 [15]. The subject of this retrospective cohort study was 674 CDH patients who were born between January 2006 and December 2010 in 109 institutions. In these, 444 CDH patients survived to discharge. Among these survivors, 182 cases who were treated in the 9 participating institutions were subject to this retrospective observational study. The 9 institutions were the high volume centers which belonged to The Japanese Congenital Diaphragmatic Hernia Study Group and declared intentions to participating in the study. Hence, inclusion criteria of this study were (1) CDH infants, (2) born between January 2006 and December 2010, (3) treated in 9 participating institutions, (4) survived to discharge. There were no exclusion criteria based on the side of hernia, associated anomalies, prenatally detection or ECMO use. Medical records during follow-up were retrospectively reviewed. The study was performed after being approved by the institutional ethics committee of Chiba University (No. 1647) and the independent ethics committees of 8 other participating institutions.

Data collection

We selected two primary outcomes; completion of medical therapy for GERD and incidence of antireflux surgery for GERD. In each institution, GERD was basically diagnosed by contrast study and pH monitoring with optional endoscopy. However, not the all patients underwent all these examinations mainly due to the policy of primary doctors. Operative indication of GERD was basically intractable symptoms including life-threatening complications of GERD, however, criterion of each case could not be confirmed. Furthermore, timing of surgery might be different between the participating institutions, and be on a case-by-case basis practically.

The patient demographics, including gender, gestational age, birth weight, Apgar score at 1 and 5 min, prenatal diagnosis, mode of delivery, and side of hernia were reviewed. Information about the severity of CDH including findings of liver herniation (prenatally detected herniation, occupying more than 1/3 of the thoracic space), position of the stomach, observed-to-expected lung area-to-head circumference ratio (o/e LHR), lung-to-thorax transverse area ratio (*L/T* ratio) [16], defect size of the diaphragm categorized into 4 groups (defect of <25 %, ≥ 25 and <75 %, ≥ 75 and <100 %, and agenesis), and the use of inhaled nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO) or patch for closure were also reviewed. Home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, or vasodilator administration at the time of hospital discharge, and evaluation of developmental delay at 1.5, 3 and 6 years of age were also reviewed.

Statistical analysis

The statistical analyses were performed using the JMP software program (v.9.02; SAS Inc., Cary, USA). The mean and standard deviation or median and interquartile range were used to describe continuous variables. Kaplan–Meier survival analysis and Cox proportional hazards regression were used for the analyses. Continuous data were divided in two groups by the median value. Chi-square test or Fisher's exact probability test were used for comparison. p values of <0.05 were considered statistically significant.

Results

Patient demographics

Table 1 shows patient demographics. In a total of 182 survivors, 156 cases (85.7 %) were diagnosed prenatally. Rate of left-sided herniation was 91.8 %. Cases with isolated CDH account for 92.9 %. Cases with liver-up, herniation of more than half of the stomach into the right chest, o/e LHR of less than 40, *L/T* ratio of less than 0.08, defect size of the diaphragm of more than 75 % were 27.0, 11.3, 70.9, 28.4 and 27.8 %, respectively. During therapies, iNO, ECMO, and patch for closure were used in 67.6, 5.5 and 37.8 %, respectively. Intact discharge which is defined as no home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, or vasodilator administration at discharge, was seen in 144 cases (79.1 %). There was no death during the follow-up period.

Table 1 Patient demographics

Patient number	182
Gender (male)	99/182 (54.4 %)
Gestational age (day)	264.5 ± 12.2
Birth weight (g)	2,680 ± 473
Apgar score at 1 min	5 (1–9)
Apgar score at 5 min	6 (1–10)
Prenatal diagnosis	156/182 (85.7 %)
Cesarean section at delivery, (%)	111/182 (61.0 %)
Side of hernia (left)	167/182 (91.8 %)
Isolated CDH	169/182 (92.9 %)
Liver-up (%)	41/152 (27.0 %)
Herniation of more than half of the stomach into the right chest	17/150 (11.3 %)
o/e LHR <40	129/182 (70.9 %)
L/T ratio <0.08	29/102 (28.4 %)
Defect size of the diaphragm ≥75 %	50/180 (27.8 %)
Use of iNO	123/182 (67.6 %)
Use of ECMO	10/182 (5.5 %)
Use of patch for closure	68/180 (37.8 %)
Developmental delay, at 1.5 years of age	38/145 (26.2 %)
Developmental delay, at 3 years of age	28/127 (22.0 %)
Developmental delay, at 6 years of age	7/36 (19.4 %)
Ventilatory support at discharge	22/182 (12.1 %)
Oxygen administration at discharge	6/182 (3.3 %)
Tracheotomy at discharge	4/182 (2.2 %)
Tube feeding at discharge	21/182 (11.5 %)
Vasodilator administration at discharge	16/182 (8.8 %)

CDH congenital diaphragmatic hernia, *o/eLHR* observed-to-expected lung area-to-head circumference ratio, *L/T ratio* lung-to-thorax transverse area ratio, *iNO* inhaled nitric oxide, *ECMO* extracorporeal membrane oxygenation

Medical therapies for GERD

In 182 cases of CDH, the medical therapies for GERD were performed in 23.8 % (40/168) of CDH patients, and were completed in 60.0 % (24/40) during the period of survey (Fig. 1a). Median (range) age of completion was 288 (32–1,241) days of life. In the 40 cases with medical therapy for GERD, 13 cases (32.5 %) underwent antireflux surgery. In these, 7 cases (53.8 %) completed medical therapy after surgery. By the Kaplan–Meier survival analysis, the rate of unsuccessful weaning of medical therapies was significantly correlated with prenatal detection of CDH ($p < 0.0001$), diaphragmatic defect of more than 75 % ($p = 0.0270$), use of iNO ($p = 0.0101$), and tube feeding at discharge ($p = 0.0018$). In these factors, only prenatal detection of CDH [hazard ratio (HR) 5.87, 95 % confidence interval (CI) 1.6–18.8, $p = 0.0120$] and tube feeding (HR 5.04, 95 % CI 1.3–33.1, $p = 0.0164$) were significantly correlated with the rate of unsuccessful weaning of medical therapy by multivariable analysis (Table 2). Patients with prenatal detection tended to have worse indices about the severity of CDH compared to cases without prenatal detection; Apgar score at 5 min of <6 (48.7 vs 11.5 %, $p < 0.0001$), diaphragmatic defect of more than 75 % (31.4 vs 4.2 %, $p = 0.0055$) and patch closure (42.6 vs 8.0 %, $p < 0.0001$). These trends

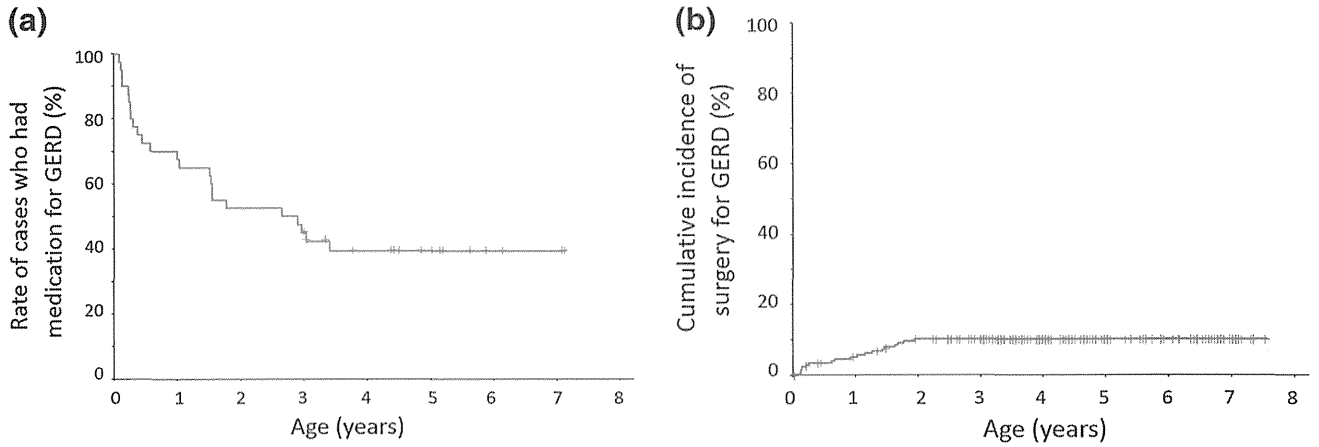

Fig. 1 **a** Kaplan–Meier curve of weaning from medical therapy for gastroesophageal reflux disease (GERD). *Longitudinal axis* represents the rate of the cases who had medication for GERD. In 40 cases, who had the medical therapies for GERD, 16 case (40.0 %) could not complete it during the period of survey. **b** Kaplan–Meier curve of incidence of antireflux surgery. *Longitudinal axis* represents the cumulative incidence of antireflux surgery. Antireflux surgery was performed eventually in 10.7 % of cases with congenital diaphragmatic hernia

Table 2 Univariate and multivariable analysis for the risk of unsuccessful weaning from medical therapy and the risk of future need of surgery for gastroesophageal reflux disease associated with congenital diaphragmatic hernia

	Univariate analysis	Multivariable analysis	
	p value	HR (95 % CI)	*p* value
The risk of unsuccessful weaning from medical therapy for GERD			
Prenatal diagnosis	<0.0001	5.9 (1.6–18.8)	0.0120
Diaphragmatic defect ≥75 %	0.0270	1.7 (0.6–5.3)	0.3104
Use of iNO	0.0101	2.5 (0.9–6.5)	0.0749
Tube feeding at discharge	0.0018	5.0 (1.3–33.1)	0.0164
The risk of future need of surgery for GERD			
GA, >265 day	0.0400	4.8 (1.5–21.1)	0.0063
Apgar score at 5 min, <6	0.0135	1.8 (0.6–6.1)	0.2818
Diaphragmatic defect ≥75 %	0.0006	4.3 (1.6–12.9)	0.0051

GERD gastroesophageal reflux disease, *iNO* inhaled nitric oxide, *HR* hazard ratio, *CI* confidence interval, *GA* gestational age

were not seen in patients with/without tube feeding at discharge. Instead, patients with tube feeding at discharge tended to have developmental delay during follow-up (at 3 years of age, 61.5 vs 17.5 %, $p = 0.0013$), while overall incidence of developmental delay was 26.2 %. Furthermore, the rate of antireflux surgery in patients with/without developmental delay was 25.0 and 6.1 %, respectively ($p = 0.008$).

The effects of the institutional biases on weaning from medical therapy for GERD were assessed. Rate of completion of the medical therapy in the institutions of high rate of prenatal diagnosis (94.4–100.0 %, in 4 institutions) and that of low rate (74.1–80.0 %, in 5) were 11.4 and 9.6 %, respectively ($p = 0.7002$). Similarly, rate of completion of the medical therapy in the institutions of high rate of tube feeding (20.8–30.8 %, in 3 institutions) and that of low rate (0–11.1 %, in 6) were 50.0 and 66.7 %, respectively ($p = 0.2918$).

Surgery for GERD

The rate of surgery for GERD was 10.7 % (18/169) of CDH survivors. Median (range) age at the surgery was 359 (42–710) days of life (Fig. 1b). By the Kaplan–Meier survival analysis, the rate of surgery was significantly correlated with gestational age over 265 days (median value) ($p = 0.0040$), liver herniation ($p = 0.0035$), herniation of more than half of the stomach into the right chest ($p < 0.0001$), the lung-to-thorax transverse area ratio less than 0.08 ($p = 0.0160$), Apgar score at 5 min less than 6 ($p = 0.0135$), diaphragmatic defect of more than 25 % ($p = 0.0359$), more than 75 % ($p = 0.0006$) (Fig. 2) and agenesis ($p = 0.0172$), and developmental delay at 3 years of age ($p = 0.0032$). Multivariable analysis was conducted for the only factors which satisfy both statistical significance ($p < 0.05$) and low missing value (<15 %), because too many factors had statistical significance. Accordingly, gestational age (HR 4.78, 95 % CI 1.5–21.1, $p = 0.0063$) and diaphragmatic defect of more than 75 % (HR 4.3, 95 % CI 1.6–12.9, $p = 0.0051$) were significantly correlated with the rate of surgery (Table 2). In the 50 cases with diaphragmatic defect of more than 75 %, 16 cases

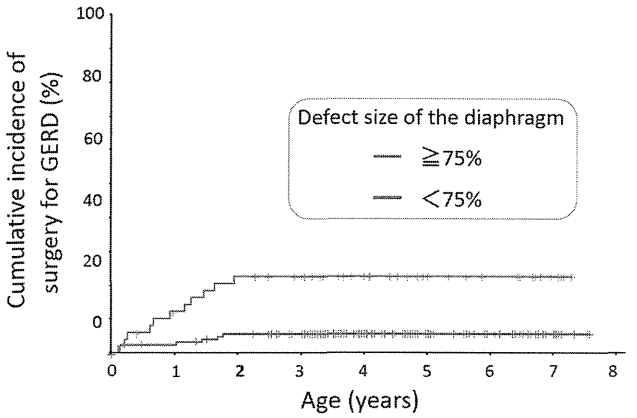

Fig. 2 Kaplan–Meier curve of incidence of antireflux surgery between the cases with diaphragmatic defect of ≥75 and <75 %. Longitudinal axis represents the cumulative incidence of antireflux surgery. Incidence of surgery was significantly higher in the cases with diaphragmatic defect of ≥75 % ($p = 0.0006$)

(32.0 %) actually had surgery (11 cases) or medication for longer than 3 years (9 cases, data overlap).

The institutional bias of gestational age was assessed, as follows. Median rate of patients with gestational age of >265 day in each institution was 48.1 %. Incidences of antireflux surgery in the institutions of extremely high rate of gestational age of >265 day (67.9 and 82.9 %, in 2 institutions) and that of extremely low rate (29.2 and 38.9 %, in 2) were 23.2 and 2.5 %, respectively ($p = 0.0046$).

Discussion

Gastroesophageal reflux disease associated with CDH is one of the considerable problems. Although the rate of GERD in CDH patients varies according to study designs, nearly 40 % of CDH survivors are thought to have symptomatic GERD, and half of them require antireflux surgery [1]. Meanwhile, some reports have revealed that natural history of GERD associated with CDH has the tendency to resolve without surgery, as well as isolated GERD [9, 14, 15]. In this study, 11 % of total cases underwent surgery by the age of 2 years, while 60 % of patients who had medical therapies for GERD completed it by the age of 3 years. In CDH survivors, GERD cases who need antireflux surgery and the cases with the tendency to resolve without surgery were mixed. Therefore, we purposed to know the natural history and the risk factors of GERD associated with CDH in the present study.

The multivariable analysis showed that the risk factors of unsuccessful weaning from medical therapies were prenatal detection of CDH and tube feeding at discharge. Because prenatal diagnosis was associated with severity of CDH including defect size of the diaphragm, patients with prenatal diagnosis might have severer GERD, resulting in long duration of medication for GERD. Tube feeding at discharge is usually used for not only the cases with severe GERD, but also the cases with difficulty in oral feeding due to developmental problems. Both of 2 factors might have influenced on long duration of medication for GERD, because patients with tube feeding at discharge actually tended to have developmental delay.

The other multivariable analysis shows that the risk factors of future need of antireflux surgery are gestational age of >265 day and diaphragmatic defect of more than 75 %. Institutional bias might be one of the possible interpretation that long gestational age is linked the necessity of antireflux surgery, because antireflux surgery was performed more frequently in the institutions which had higher rate of patients of gestational age of >265 day. Large diaphragmatic defect seems to be the reasonable and specific risk factor of future need for surgery, and consistent with the previous reports [7, 8]. And, it is basically consistent with the result that prenatal diagnosis is linked the duration of medical therapy for GERD, because patients with prenatal diagnosis tended to have large diaphragmatic defect. Meanwhile, tube feeding at discharge was the specific risk factor for medical therapy for GERD, possibly affected by the factor of developmental delay.

The merit of the present study is that we assessed the risk of severe GERD in CDH by the method which can evaluate the data on the time course using Cox regression model. By conducting this study, useful data for selecting the therapeutic strategies for GERD in CDH should be obtained. As a result, patients with the large diaphragmatic defect are associated with severe GERD. These data lead us to think of the additional antireflux surgery at the first operation for CDH. The same concept had been postulated since early 1990s [4], but is still controversial. The multicenter retrospective study conducted by French group showed a significant relationship between prophylactic fundoplication performed during initial diaphragmatic repair and survival without disordered growth [17]. They concluded that prophylactic fundoplication can prevent growth disorder in infants with CDH requiring a patch repair. However, randomized controlled study conducted by Maier et al. [18] revealed that there was no significant difference of GERD symptoms and development of body weight in the first 2 years between cases with regular hernia closure and cases with additional fundoplication at hernia repair. They concluded that simultaneous fundoplication at the time of primary CDH repair cannot be recommended in all patients with CDH. Because this prospective study involved all the left-sided CDH patients with various severities, usefulness of prophylactic fundoplication for limited cases with some risk factors is still

unclear. In the present study, the cases with diaphragmatic defect of more than 75 % were proposed as the risk factor of future need of antireflux surgery. But, only 32.0 % of patients with this risk factor actually had antireflux surgery or medication of longer than 3 years. Further studies are still needed to discuss about the pros and cons of prophylactic fundoplication.

The most considerable limitation of this study is that strategies for both CDH and GERD were not unified; all the factors including diagnostic method of GERD, severity of GERD, type of drugs used, the indication, and the procedure of antireflux surgery. This means that all the results were possibly influenced by each institutional policy. These limitations resulted from our study design to collect as much patients as possible by multicenter study. To elucidate the risk of GERD in CDH, the present study will need to be supported by further studies. However, the biases which this study contains should be avoided in the future. Hence, further studies should be designed to treat the patients prospectively. Otherwise, at least unifying the diagnostic criteria of GERD is needed in retrospective studies.

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Conflict of interest The authors declare that they have no conflicts of interest.

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Original Article

Outcome of congenital diaphragmatic hernia with indication for Fontan procedure

Nobuko Shiono,[1] Noboru Inamura,[1] Shigehiro Takahashi,[4] Kouji Nagata,[6] Yuji Fujino,[2] Masahiro Hayakawa,[7] Noriaki Usui,[3] Hiroomi Okuyama,[8] Yutaka Kanamori,[5] Tomoaki Taguchi[6] and Hisanori Minakami[9]

[1]*Department of Pediatric Cardiology, Osaka Medical Center and Research Institute for Maternal and Child Health,* [2]*Intensive Care Unit, Osaka University Hospital,* [3]*Department of Pediatric Surgery, Osaka University, Graduate School of Medicine, Osaka,* [4]*Division of Neonatology, Department of Maternal and Perinatal Medicine,* [5]*Division of Surgery, Department of Surgical Subspecialties, National Center for Child Health and Development, Tokyo,* [6]*Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka,* [7]*Department of Maternal and Perinatal Care Center, Nagoya University Hospital, Nagoya,* [8]*Department of Pediatric Surgery, Hyogo College of Medicine University, Hyogo and* [9]*Department of Obstetrics and Gynecology Hokkaido University Graduate School of Medicine, Sapporo, Japan*

Abstract ***Background***: The aim of this study was to clarify the outcome of patients with cardiovascular malformation (CVM) among those with congenital diaphragmatic hernia (CDH) who are indicated for the Fontan procedure.

Methods: The subjects included 76 CDH patients with CVM recruited from a national survey of 614 CDH patients. The outcomes were evaluated between two groups divided according to indication for the Fontan procedure. Patients with functional univentricular disease were considered to be candidates for the Fontan procedure.

Results: Sixteen (21.1%) of the 76 patients were candidates for the Fontan procedure, accounting for 2.6% of all 614 patients with CDH. None of these patients, however, underwent the Fontan procedure. Among the 16 patients, the absence of obstruction of the left ventricular outflow tract (LVOTO) was significantly associated with better 90 day survival (71.4%, 5/7, for those without LVOTO vs 0.0%, 0/9, for those with LVOTO, $P = 0.0007$). After excluding 22 patients with chromosomal and/or genetic abnormalities or syndromes, the 90 day survival rate was significantly better in neonates without than with indication for the Fontan procedure (62.5%, 25/40 vs 28.6%, 4/14, $P = 0.0271$).

Conclusions: Patients with indications for the Fontan procedure are rare, and the outcome of patients with LVOTO among those with CDH is especially poor.

Key words cardiovascular malformation, congenital diaphragmatic hernia, Fontan procedure, national survey.

The Fontan procedure is a surgical procedure used to treat tricuspid atresia, devised by Fontan in 1971. It is a special technique that directly connects the pulmonary artery to the systemic venous system. Strict indications, called "Fontan's ten commandments", have been proposed to identify patients who are eligible to undergo this procedure.[1] The indications have been widened, however, to include patients with single ventricles (SV) and hypoplastic left hearts in addition to tricuspid atresia due to modifications of the procedure.[2]

Congenital diaphragmatic hernia (CDH) is a severe disease causing pulmonary hypoplasia due to impaction of the abdominal organs in the thoracic cavity, twisting of the heart to the intact side and compression of the lungs on both the intact and affected sides.[3] In Japan, the survival rate of patients with CDH alone surpasses 80%,[4] but the outcome of CDH patients with cardiovascular malformations (CVM) is poor.[5] Although it is generally thought that the outcome of patients with both CDH and CVM, such as functional SV, is especially poor, attempts to improve these outcomes have been made,[5–7] and Japanese physicians appear to be active in the treatment of such patients. The effects of treatment on the outcome of CDH patients with CVM who are potential candidates for the Fontan procedure, however, remain to be studied.

The aim of this study was therefore to clarify the prevalence and outcomes of patients with CVM among those with CDH who are indicated for the Fontan procedure.

Methods

This study was conducted after obtaining the approval of the independent ethics committees of our institution (approval number of 468) and five other institutions. The data obtained from 72 facilities that consented to a questionnaire survey targeted to 159 facilities, including facilities authorized by the

Correspondence: Nobuko Shiono, MD, Department of Pediatric Cardiology, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodo-cho, Izumi, Osaka 594-1101, Japan. Email: salt0226@yahoo.co.jp

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Japanese Society of Pediatric Surgeons, education-related facilities and Centers for Maternal, Fetal and Neonatal Medicine, in 2011 were retrospectively evaluated. There were 614 patients with CDH born between 2006 and 2010. The overall profiles of the 614 patients have been previously described.[4] A total of 108 (17.6%) of the 614 patients had CVM.[4] In this study, 76 CDH patients with CVM were evaluated after excluding 32 patients, including 21 patients with a patent ductus arteriosus (PDA) alone, six patients with both PDA and atrial septal defect (ASD), three patients with ASD alone, one patient with mild pulmonary valvular stenosis and ASD and one patient with a right-sided aortic arch.[5] Therefore, the 76 study subjects accounted for 12.5% of the 614 CDH patients.[5]

Type of cardiac disease, patient respiratory status, treatment(s) used for CDH and outcome were evaluated by dividing the 76 subjects into two groups: those with and those without indications for the Fontan procedure (Fontan and non-Fontan candidates, respectively). The primary indication for the Fontan procedure was univentricular disease. For example, patients with SV, hypoplastic left heart syndrome (HLHS) or pulmonary atresia, in addition to those with tricuspid atresia, were considered to be typical candidates for the Fontan procedure.

In an analysis of the association between type of cardiac disease and outcome, the patients were classified into four subgroups based on cardiac morphology: patients with left ventricular outflow tract obstruction (LVOTO), patients with right ventricular outflow obstruction (RVOTO), patients with pulmonary venous obstruction (PVO) and patients with PDA-dependent disease. The therapeutic strategy was classified as either positive or palliative.

Statistical analysis was done using chi-squared test, two-sample *t*-test and Wilcoxon test, as appropriate. The level of significance was set at $P < 0.05$.

Results

Of the 76 CDH patients with CVM, 16 and 60 were considered to be eligible or not eligible for the Fontan procedure, respectively (Table 1). None of the 16 patients, however, underwent the Fontan procedure. Among the patients with CVM in the Fontan candidate (FC) group, HLHS and SV were noted in seven (44%) and six (38%) patients, respectively (Fig. 1; Table 2). In the non-Fontan (non-FC) candidate group, the following CVM were noted: ventricular septal defect (VSD) in 25 patients (41%), tetralogy of Fallot/double outlet right ventricles accompanied by RVOTO (TOF/DORV with RVOTO) in 12 (20%) and DORV without RVOTO in eight patients (13%).

No significant differences were noted in Apgar score, number of patients with prenatal diagnosis of CDH, gestational age at birth, birthweight, side of CDH or the presence of chromosomal or genetic abnormalities between the FC and non-FC groups (Table 1). Surgery for CDH was performed in 63% of the patients in the non-FC group and in 38% of the patients in the FC group ($P = 0.064$). The frequency of postnatal use of extracorporeal membrane oxygenation (ECMO) did not differ significantly between the two groups. The highest PaO_2 was significantly lower and the lowest $PaCO_2$ and the lowest oxygen index (OI) were significantly higher in the FC group than in the non-FC group. Neither the rate of survival >90 days (31.3% in the FC group vs 46.7% in the non-FC group) or 2 years nor the rate of intact discharge differed between the two groups. After excluding 22 patients (two in the FC-group and 20 in the non-FC group) with chromosomal and/or genetic abnormalities or syndromes, however, the surgical rate of CDH in the non-FC group increased from 63.3% (38/60) to 75.0% (30/40), which was significantly higher than that of the 35.7% (5/14) observed in the FC group ($P = 0.0091$; Table 2). The rates of 90 day

Table 1 Subject clinical characteristics ($n = 76$)

		FC group ($n = 16$) n (%) or mean ± SD	Non-FC group ($n = 60$) n (%) or mean ± SD	P
Characteristics	Apgar score at 1 min (0–5)	12 (92.3)	46 (85.2)	0.4740
	Apgar score at 5 min (0–5)	9 (75.0)	34 (65.4)	0.5150
	Left-sided CDH	13 (81.2)	55 (91.7)	0.3150
	Prenatal diagnosis for CDH	14 (87.5)	48 (80.0)	0.4760
	Gestational age (weeks)	36.0 ± 0.5	36.7 ± 0.3	0.3020
	Birthweight (g)	2235 ± 149	2294 ± 77	0.7240
	Chromosomal or genetic abnormalities, syndromes	2 (12.5)	20 (33.3)	0.0820
Operation	Surgical repair of CDH	6 (37.5)	38 (63.3)	0.0640
Respiratory status after birth	Use of ECMO	2 (12.5)	3 (5)	0.3180
	Highest PaO_2 (mmHg)	53.0 ± 41.9	113.7 ± 101.3	0.0484*
	Lowest $PaCO_2$ (mmHg)	71.9 ± 11.4	43.5 ± 5.7	0.0291*
	Lowest OI	44.2 ± 6.4	23.6 ± 3.1	0.0056*
Outcome	90 day survival	5 (31.3)	28 (46.7)	0.2603
	2 year survival	2 (12.5)	12 (20.0)	0.4759
	Intact discharge rate	1 (6.3)	12 (20.0)	0.1550

*$P < 0.0.5$. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FC, candidates for the Fontan procedure; intact discharge, discharge without tracheostomy, oxygen, mechanical ventilation, parenteral nutrition or drugs (e.g. pulmonary vasculature dilators); non-FC, not candidates for the Fontan procedure; OI, oxygenation index.

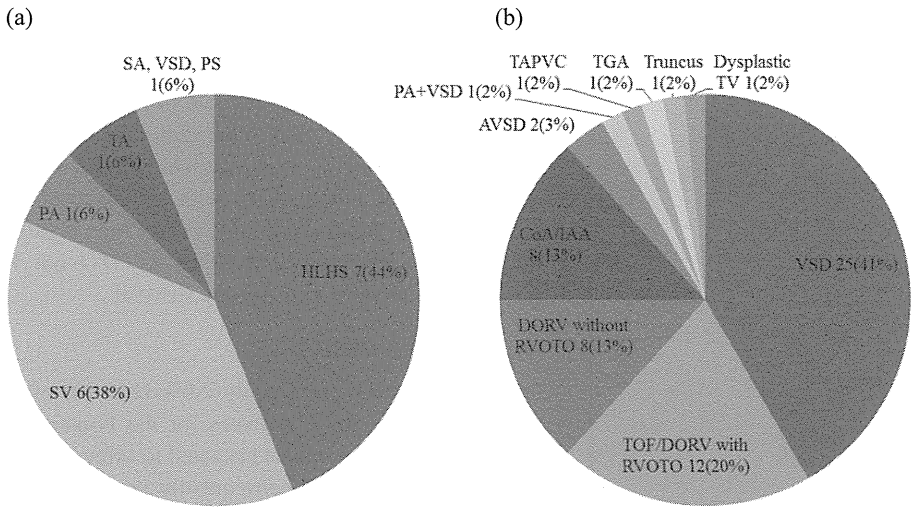

Fig. 1 Cardiovascular malformations in (a) 16 congenital diaphragmatic hernia (CDH) patients with indication for the Fontan procedure and (b) 60 CDH patients without indications for the Fontan procedure. AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricle outlet obstruction; SA, single atrium; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

survival, 2 year survival and intact discharge increased considerably to 62.5% (25/40), 27.5% (11/40) and 27.5% (11/40), respectively, in the non-FC group, although they did not change in the FC group (to 28.6%, 4/14; 14.3%, 2/14; and 7.1%, 1/14, respectively). Therefore, the differences in outcome with respect to 90 day survival rate (28.6%, 4/14 vs 62.5%, 25/40, $P = 0.0271$) became marked and significant after excluding 22 patients with chromosomal and/or genetic abnormalities or syndromes (Table 2).

The details of each patient in the FC group are given in Table 3. CDH was right-sided in three patients, one of whom had situs inversus viscerum. Complications other than CVM were noted in five patients: corpus callosum agenesis in two, Fryns syndrome in one, 18 trisomy in one and situs inversus viscerum in one. In these five patients, a positive therapeutic approach was chosen, except in the patient with Fryns syndrome. Two patients underwent ECMO without successful results. CDH was treated surgically in six patients, two of whom survived for 2 years. Palliative surgery for CVM was performed in four patients, including the use of the Glenn procedure in one patient (patient 14) who died 5 months after operation. The remaining three patients underwent shunting surgery only.

All of the five patients who survived >90 days underwent radical surgery for CDH, and the two patients who had long-term survival both underwent radical surgery for CDH and palliative surgery for CVM.

Table 2 Subjects without genetic abnormalities ($n = 54$)

		FC group ($n = 14$) n (%) or mean ± SD	Non-FC group ($n = 40$) n (%) or mean ± SD	P
Characteristics	Apgar score at 1 min (0–5)	10 (90.9)	28 (80.0)	0.3780
	Apgar score at 5 min (0–5)	7 (70.0)	20 (58.8)	0.5183
	Left sided CDH	12 (85.7)	38 (95.0)	0.2370
	Prenatal diagnosis for CDH	12 (85.7)	31 (77.5)	0.4990
	Gestational age (weeks)	35.8 ± 2.3	36.9 ± 2.5	0.1816
	Birthweight (g)	2234 ± 486	2434 ± 570	0.3742
Operation	Surgical repair of CDH	5 (35.7)	30 (75.0)	0.0091*
Respiratory status after birth	Use of ECMO	2 (14.3)	2 (5)	0.2829
	Highest PaO_2 (mmHg)	55.7 ± 42.8	138.0 ± 114.4	0.0276*
	Lowest $PaCO_2$ (mmHg)	61.1 ± 37.8	43.2 ± 41.7	0.0869
	Lowest OI	41.8 ± 24.1	19.5 ± 14.9	0.0047*
Outcome	90 day survival	4 (28.6)	25 (62.5)	0.0271*
	2 year survival	2 (14.3)	11 (27.5)	0.3005
	Intact discharge rate	1 (7.1)	12 (30.0)	0.0601

*$P < 0.0.5$. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FC, candidates for the Fontan procedure; intact discharge, discharge without tracheostomy, oxygen, mechanical ventilation, parenteral nutrition or drugs (e.g. pulmonary vasculature dilators); non-FC, not candidates for the Fontan procedure; OI, oxygenation index.

Table 3 Fontan candidate characteristics ($n = 16$)

Case	CVM	Side of CDH	Complication	Treatment strategy	ECMO	Operation for CDH	Operation for CVM	90 day survival	2 year survival
1	HLHS	L	–	Palliative	–	–	–	No	No
2	HLHS	L	–	Positive	–	–	–	No	No
3	HLHS	L	–	Positive	–	–	–	No	No
4	HLHS	L	–	Positive	+	+	–	No	No
5	HLHS	L	Agenesis of the corpus callosum	Positive	–	–	–	No	No
6	HLHS, PA, DORV	L	–	Palliative	–	–	–	No	No
7	HLHS, TAPVC	L	–	Positive	+	–	–	No	No
8	SA, VSD, PS	R	–	Positive	–	–	–	No	No
9	SV, CoA	L	Agenesis of the corpus callosum	Positive	–	–	–	No	No
10	SV, IAA	L	–	Positive	–	–	–	No	No
11	SA, SV	L	Fryns syndrome	Palliative	–	–	–	No	No
12	SV, DORV	R	Trisomy 18	Positive	–	+	–	Yes	No
13	PA	L		Positive	–	+	+	Yes	No
14	TA	L		Positive	–	+	+	Yes	No
15	SA, SV, TAPVC, PS	R	Situs inversus	Positive	–	+	+	Yes	Yes
16	SV	L		Positive	–	+	+	Yes	Yes

ASD, atrial septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of aorta; CVM, cardiovascular malformations; DORV, double outlet right ventricle; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; IAA, interruption of aortic arch; SA, single atrium; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

The therapeutic strategy (palliative or radical), presence of malformations other than CVM and the type of cardiac deformity according to 90 day survival of the 16 FC patients are listed in Table 4. Neither the rate of palliative approach nor the presence of complications other than CVM differed significantly between the five and 11 patients who did and did not survive >90 days. All of the nine patients with LVOTO had PDA-dependent disease, and the absence of LVOTO was significantly associated with 90 day survival. Neither RVOTO nor PVO was significantly associated with 90 day survival.

Discussion

In the present study 2.6% (16/614) of the CDH patients were potentially candidates for the Fontan procedure. In this study, many physicians hesitated to offer the Fontan procedure to these patients, and consequently none of the patients underwent the Fontan procedure. In addition, all of the nine patients with LVOTO died within 90 days of life.

CDH is rare, present in only 2.4–2.5 of 10 000 births,[6,7] while CVM are relatively common, present in nine of 1000 births.[8] The overall prevalence of CVM was 17.6% (108/614) in the present subjects with CDH,[4] and the prevalence of CVM other than PDA, ASD, pulmonary valvular stenosis or a right-sided aortic arch was 12.4%, consistent with previous studies.[9,10] According to Pober *et al.*, CVM including ASD were present in 11.3% (23/203) of their study patients with CDH, while ASD and/or VSD and SV accounted for 56% (13/23) and 4% (1/23) of the CVM observed, respectively.[11] According to Calzolari *et al.*, ASD and/or VSD and SV accounted for 48% (634/1328) and 3% (43/1328) of their study patients with CDH complicated by CVM, respectively.[12] In the present 108 CDH

Table 4 Fontan candidate characteristics vs 90 day survival

	90 day survival		*P*
	Yes ($n = 5$)	No ($n = 11$)	
Palliative strategy	0	3	0.1100
Presence of other anomalies	2	3	0.6100
PDA-dependent disease	1	9	0.0160
LVOTO and PDA-dependent disease	0	9	0.0007
PDA-dependent disease without LVOTO	1	0	0.1155
Neither LVOTO nor PDA-dependent disease	4	2	0.0166
Absence of LVOTO	5	2	0.0007
RVOTO	2	2	0.3600
PVO	1	1	0.5500

Other anomalies included Fryns syndrome, trisomy 18, situs inversus and agenesis of the corpus callosum. CoA, coarctation of aorta; HLHS, hypoplastic left heart syndrome; IAA, interruption of aortic arch; LVOTO, left ventricular outflow tract obstruction including HLHS, CoA, and IAA; PA, pulmonary atresia; PDA-dependent disease, patent ductus arteriosus-dependent disease including HLHS, CoA, IAA and PA; PS, pulmonary stenosis; PVO, pulmonary venous obstruction including TAPVC; RVOTO, right ventricular outflow tract obstruction including PA and PS; TAPVC, total anomalous pulmonary venous connection.

patients with CVM, including the 32 patients excluded from the present analysis, ASD and/or VSD and SV accounted for 36% (39/108) and 5.6% (6/108) of all CVM, respectively. Therefore, patients with CDH are consistently more likely to have CVM compared with neonates without CDH. This study is the first to demonstrate the prevalence of indications for the Fontan procedure among patients with CDH. Among the 614 CDH patients, 16 (2.6%) had CVM that were considered to be potential indications for the Fontan procedure. In contrast, the frequency of Fontan candidates is 0.045% among the general population, in which the frequency of CVM is 0.96%.[13] Thus, patients with CDH have a >10-fold higher risk of CVM that are potential indications for the Fontan procedure compared with the general population. In addition, the frequency of Fontan candidates was several fold higher in patients with CDH and CVM than in patients with CVM but not with CDH: 16 (14.8%) per 108 patients including 32 excluded from the present study versus 4.7% in the general population with CVM.[13]

Although the clinical outcomes, including the 90 day and 2 year survival and intact discharge rates, did not differ statistically between the 16 and 60 patients with and without indications for the Fontan procedure, respectively, these indices were consistently better among the 60 patients without indications for the Fontan procedure than among the 16 patients with indications for the Fontan procedure despite the fact that as many as one-third of these 60 patients had chromosomal abnormalities and/or genetic abnormalities or syndromes. After excluding 22 patients with these abnormalities, the surgical rate of CDH increased and the 90 day and 2 year survival rates improved considerably in the non-FC group, resulting in significantly better outcome with respect to 90 day survival in the non-FC group than in the FC-group. Therefore, better outcome can be expected in patients with both CDH and CVM without indication for the Fontan procedure when chromosomal and/or genetic abnormalities or syndromes are absent. The highest PaO_2 was significantly lower and the lowest $PaCO_2$ and OI were more severe in the patients with CVM with indications for the Fontan procedure in this study. It is possible that these factors were responsible for the poor outcome observed in this group. These factors, however, generally do not serve as indices of survival, perhaps because blood gas data do not reflect the state of respiration, but rather the volume of the pulmonary blood flow, in patients with cyanotic heart disease.

The surgical rate of CDH was found to be significantly lower in the FC group than in the non-FC group after excluding the 22 patients with chromosomal and/or genetic abnormalities or syndromes. We anticipated that a certain type of CVM in patients with indications for the Fontan procedure would predict poor outcome. Indeed, outcome was poorer in the nine patients with LVOTO (patients 1–7, 9, 10): none had a 90 day survival. Although therapeutic strategy was positive in seven of the patients with LVOTO, no patients were able to undergo radical treatment for CDH or palliative surgery for CVM in this study. This suggests that a positive therapeutic strategy is not indicated at present in patients with CDH and LVOTO.

The left heart system is small in fetuses and neonates with left-sided CDH.[14–25] Direct compression of the lungs and left atrium by abdominal organs prolapsing into the thoracic cavity, disturbance of the blood flow passing through the foramen ovale and a decreased pulmonary blood flow are considered to be complex factors causing a decrease in the amount of blood flowing into the LV.[23] The LV mass index is significantly lower in fetuses with CDH than in those without CDH.[21] When the LV is too small to output sufficient volume in neonates, the RV successfully compensates for the low output by directing blood through the ductus arteriosus, which is kept patent by nitric oxide and prostaglandin E1.[22] The poor outcomes observed in the present patients with LVOTO may be explained by insufficient maintenance of hemodynamics due to the small size of the LV. In addition to the heart disease itself, changes in hemodynamics due to CDH in the fetal period may have further worsened LV function. These factors may have hindered repair of CDH and CVM in the patients with LVOTO. In contrast, among the four patients with RVOTO (patients 6, 8,13,15), both radical treatment for CDH and palliative surgery for CVM were possible in two patients (patients 13, 15). Because the LV function was nearly normal, it was relatively easy to maintain hemodynamics in the patients with RVOTO. The positive therapeutic strategy was undertaken in seven of the nine patients with LVOTO

Surgical treatment for CVM may have led to the longer 90 day survival observed in some patients, although none of the 16 patients underwent the Fontan procedure due to the severity of their disease. Pulmonary function is an important factor determining the feasibility of the Fontan procedure.[1] Preventing the persistence of chronic lung disease and chylothorax, the occurrence of gastroesophageal reflux and the persistence of pulmonary hypertension, however, was often difficult, even after surgical treatment for CDH. Patient 14 died early from chronic lung problems following the Glenn procedure.

Many patients with heart disease complicated by CDH are diagnosed prenatally. Radical treatment may be initiated promptly after birth in such patients, but the outcome of patients with heart disease with indications for the Fontan procedure remained poor in this study, and only a few such patients are able to survive until palliative surgery for heart disease (I. Adatia, unpubl. data, 2004), as confirmed in the present study. The outcomes were especially poor in the patients with LVOTO. The present results have revealed a problem in how to determine how extensively patients with indications for the Fontan procedure should be treated. Systematic large studies are therefore needed to address this issue.

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