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The outcomes of patients with congenital diaphragmatic
hernia with indications for the Fontan procedure: Results
of national survey in Japan

(先天性横隔膜ヘルニアを合併したフォンタン適応心疾患の
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北 海 道 大 学

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Original article

Clinical investigations

Title: The outcomes of patients with congenital diaphragmatic hernia with indications for the

Fontan procedure

Running title: Outcomes of CDH with Fontan Indication

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Abstract

Background: To clarify the outcomes of patients with cardiovascular malformations (CVMs) among those with congenital diaphragmatic hernia (CDH) who are indicated for the Fontan procedure.

Methods: The study subjects included 76 CDH patients with CVMs recruited from a national survey of 614 CDH patients. The outcomes were evaluated between two groups divided according to the indication for the Fontan procedure. Patients with functional univentricular diseases 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. However, none of these patients 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 outcomes of patients with LVOTO among those with CDH are especially poor.

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

Introduction

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 procedure¹. However, the indications have been widened to include patients with single ventricles and hypoplastic left hearts in addition to tricuspid atresia due to modifications of the procedure².

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 sides³. In Japan, the survival rate of patients with CDH alone surpasses 80%⁴; however, the outcomes of CDH patients with cardiovascular malformations (CVMs) are poor⁵. While it is generally thought that the outcomes of patients with both CDH and CVMs, such as functional single ventricles, are especially poor, attempts to improve these outcomes have been made⁵⁻⁷ and Japanese physicians appear to be active in the treatment of such patients. However, the effects of treatment on the outcomes of CDH patients with CVMs who are potential candidates for the Fontan procedure remain to be studied.

This study aimed to clarify the prevalence and outcomes of patients with

cardiovascular malformations (CVMs) among those with congenital diaphragmatic hernia 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 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 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.

The type of cardiac disease, the patient's respiratory status, treatment(s) used for

CDH and the outcomes 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 single ventricles (SVs), hypoplastic left heart syndrome (HLHS) or pulmonary atresia, in addition to those with tricuspid atresia (TA), were considered to be typical candidates for the Fontan procedure.

In an analysis of the association between the type of cardiac disease and the outcome, the patients were classified into four subgroups based on the 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.

The statistical analysis was performed using the χ^2 -test, the two-sample t-test and Wilcoxon's test, as appropriate. The level of significance was set at $p < 0.05$.

Results

Of the 76 CDH patients with CVMs, 16 and 60 were considered to be eligible or not eligible for the Fontan procedure, respectively (Table 1). However, none of the 16 patients

underwent the Fontan procedure. Among the patients with CVMs in the Fontan candidate (FC) group, HLHS and SV were noted in seven (44%) and six (38%) patients, respectively (Figure 1 and Table 2). In the non-Fontan (non-FC) candidate group, the following CVMs were noted: ventricular septal defects (VSDs) in 25 (41%) patients, tetralogy of Fallot/double outlet right ventricles accompanied by right ventricular outflow tract obstruction (TOF/DORV with RVOTO) in 12 (20%) patients and double outlet right ventricles (DORVs) without RVOTO in eight patients (13%).

No significant differences were noted in the Apgar score, number of patients with a prenatal diagnosis of CDH, gestational age at birth, birth weight, the 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 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 rates of survival more than 90 days (31.3% in the FC group vs 46.7% in the non-FC group) or two years nor the rate of intact discharge differed between the two groups. However, after excluding 22 patients (two in the FC-group and 20 in the non-FC group) with

chromosomal and/or genetic abnormalities or syndromes, 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 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 outcomes with respect to the 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 shown in Table 3. The CDH was right-sided in three patients, one of whom exhibited situs inversus viscerum. Complications other than CVM were noted in five cases: corpus callosum agenesis in two cases, Fryns syndrome in one case, 18 trisomy in one case and situs inversus viscerum in one case. In these five cases, a positive therapeutic approach was chosen, except in the case with Fryns syndrome. Two patients underwent ECMO without successful results. CDH was treated surgically in six patients, two of whom survived for two years. Palliative surgery for CVMs was performed in four patients, including the use of the Glenn procedure in one patient

(Case 14) who died five months after the operation. The remaining three patients underwent shunting surgery only.

All of the five patients who survived more than 90 days underwent radical surgery for CDH, and the two patients who exhibited long-term survival both underwent radical surgery for CDH and palliative surgery for CVMs.

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

Discussion

The present study demonstrated that 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 CVMs are relatively common, present in nine of 1,000 births⁸. The overall prevalence of CVM was 17.6% (108/614) in our sample population with CDH⁴, and the prevalence of CVMs other than PDA, ASD, pulmonary valvular stenosis or a right-sided aortic arch was 12.4%, consistent with the results of previous studies^{9,10}. According to Pober et al., CVMs 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 CVMs observed, respectively¹¹. 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, respectively¹². In our 108 CDH patients with CVMs, 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 CVMs, respectively. Therefore, patients with CDH are consistently more likely to have CVMs compared with neonates without CDH. This study is the first to demonstrate how often patients with CDH have potential indications for the Fontan procedure. Among the 614 CDH patients, 16 (2.6%) had CVMs that were considered to be potential indications for the Fontan procedure. In contrast, the frequency of Fontan candidates is 0.045% among

general population in which the frequency of CVMs is 0.96%¹³. Thus, patients with CDH have a more than 10-fold higher risk of CVMs 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 CVMs than that in patients with CVMs 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 CVMs¹³.

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 outcomes with respect to 90-day survival in the non-FC group than in the FC-group. Therefore, better outcomes can be expected in patients with both CDH and CVMs without indication for the Fontan procedure when chromosomal and/or genetic abnormalities or syndromes are absent. The highest PaO₂ was

significantly lower and the lowest PaCO₂ and OI were more severe in the patients with CVMs with indications for the Fontan procedure in this study. It is possible that these factors were responsible for the poor outcomes observed in this group. However, these factors 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 a poor outcome. Indeed, the outcomes were poorer in the 9 patients with LVOTO (Cases 1 - 7, 9, 10): none exhibited a 90-day survival. Although therapeutic strategy was positive in 7 of the patients with LVOTO, no patients were able to undergo radical treatment for CDH or palliative surgery for CVM in this study. These results suggested that the 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 left ventricle²³. The left ventricular (LV) mass index is significantly lower in fetuses with CDH than in those without CDH²¹. When the LV is too small to output enough volume in neonates, the right ventricle successfully compensates for the low output by directing blood through the ductus arteriosus, which is kept patent by NO and PGE1²². The poor outcomes observed in patients with LVOTO in this study may be explained by insufficient maintenance of hemodynamics due to the small size of the left ventricle. In addition to the heart disease itself, changes in hemodynamics due to CDH in the fetal period may have further worsened the left ventricular function. These factors may have hindered repair of CDH and CVMs in the patients with LVOTO. In contrast, among the four patients with RVOTO (Cases 6, 8,13,15), both radical treatment for CDH and palliative surgery for CVM were possible in two patients (Cases 13, 15). As 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 7 of the 9 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. The pulmonary function is an important factor determining the

feasibility of the Fontan procedure ¹. However, preventing the persistence of chronic lung disease and chylothorax, the occurrence of gastroesophageal reflux and the persistence of pulmonary hypertension was often difficult, even after surgical treatment for CDH. The patient in Case 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. However, the outcomes of patients with heart diseases 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 ²⁶, as confirmed in this study. The outcomes were especially poor in the patients with LVOTO. The results of our study 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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Figure 1. Cardiovascular malformations in 16 CDH patients with indications for the Fontan procedure and 60 CDH patients without indications for the Fontan procedure

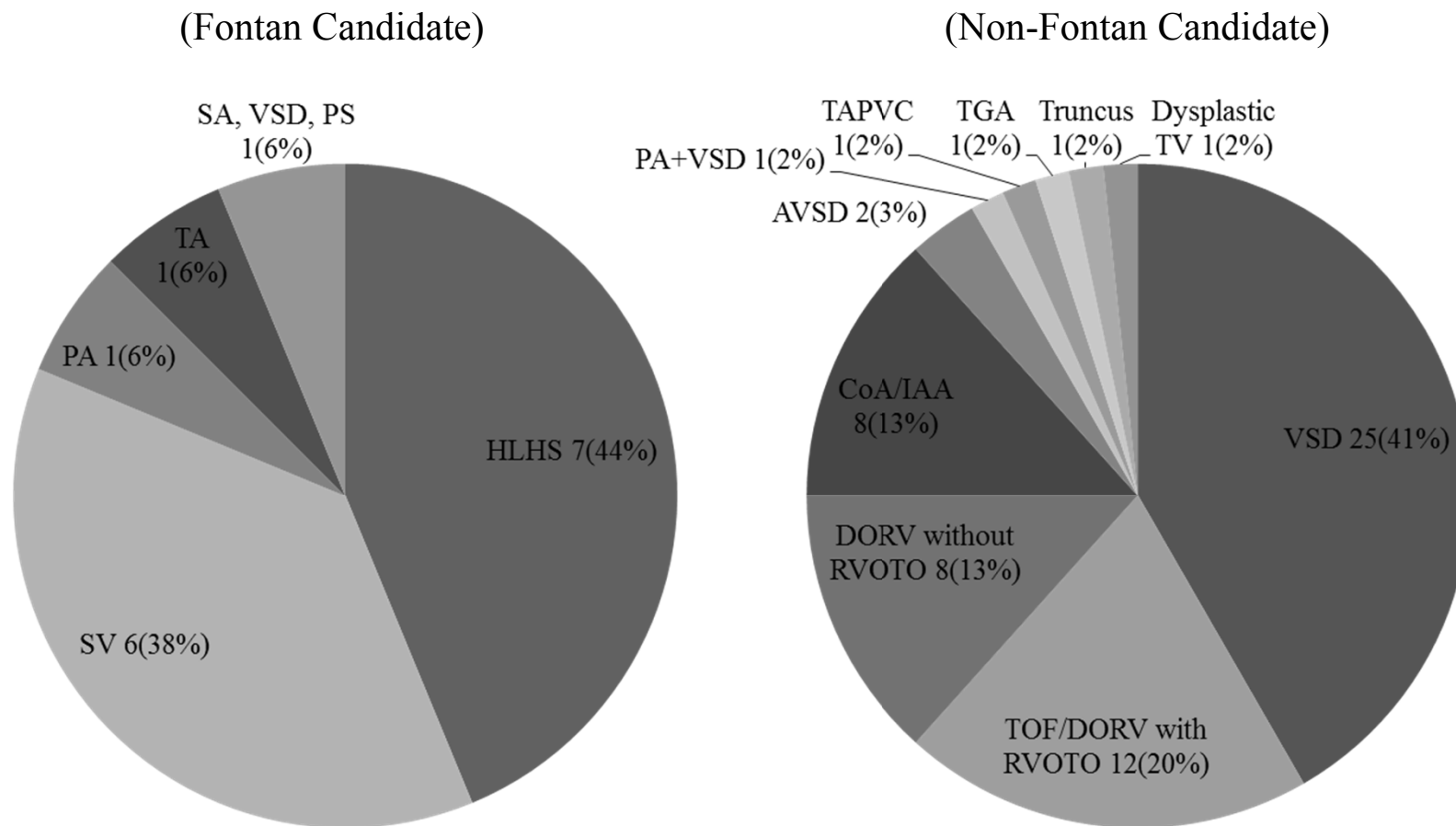


Table 1. Clinical characteristics of 76 study subjects

		Group FC n=16	Group non-FC n=60	p-value
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
	Birth weight	2,235±149g	2,294±77g	0.7240
	Chromosomal or genetic abnormalities, syndromes	2 (12.5%)	20 (33.3%)	0.0820
Operation	Surgical rate on 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*<.0.5

Table 2. Clinical characteristics of 54 study subjects without chromosomal or genetic abnormalities, syndrome

		Group FC n=14	Group non-FC n=40	p-value
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
	Birth weight	2,234±486g	2,434±570g	0.3742
Operation	Surgical rate on 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

* $P < 0.05$

Table 3. Detailed information of the 16 patients with indications for the Fontan procedure

Case	CVM	Side of CDH	Complication	Treatment strategy	ECMO	Op for CDH	Op 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

Table 4 : Treatment strategies, complications and type of cardiac disease according to survival of more than 90 days in 16 patients with indications for the Fontan procedure

	90-day survival		<i>p</i> -value
	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

**P*<.0.5