Outcome of univentricular repair in patients with Down syndrome

Takeshi Furukawa, MD,^{a,b} In-Sam Park, MD,^b Tadahiro Yoshikawa, MD,^b Tomomi Nishimura, MD,^b Yukihiro Takahashi, MD,^c Makoto Ando, MD,^c and Naoki Wada, MD^c

Objective: Total cavopulmonary connection (TCPC) is rarely performed for a functional single ventricle in children with Down syndrome; therefore, the postsurgical outcomes are not well known. We evaluated mortality and related factors after TCPC in children with Down syndrome.

Methods: Between January 2004 and March 2010 we identified 8 patients with Down syndrome among 235 patients who had undergone TCPC. The preoperative clinical course, preoperative data, and postoperative clinical course were evaluated. In addition, clinical parameters and postoperative clinical course were compared between children with Down syndrome (n = 8) and a non-Down syndrome group (n = 227).

Results: The median age at the time of TCPC was 4.1 years (range, 3.4-5.5 years), and the preoperative mean pulmonary artery pressure was 13.9 ± 1.81 mm Hg. We observed respiratory complications in 2 patients, surgical site infection in 3 patients, and chylothorax in 2 patients. No significant difference was observed in preoperative data and mortality rate (1 of 8 patients [12.5%] in the Down syndrome group; 5 of 227 patients [2.2%] in the non-Down syndrome group) between the groups of children with and without Down syndrome. However, when the postoperative clinical course was examined, the durations of intensive care unit stay ($P = .009$) and hospital stay ($P = .007$) were found to be significantly prolonged in the Down syndrome group.

Conclusions: Patients with Down syndrome tend to show prolonged recovery after TCPC. However, as opposed to previous reports, the mortality rate of patients undergoing TCPC is lower with no significant difference from that of children without Down syndrome. (J Thorac Cardiovasc Surg 2013;146:1349-52)

The Fontan operation for tricuspid atresia was first reported in 1971. Subsequently, the operation was modified several times and used for the treatment of other congenital heart diseases associated with a single functional ventricle.¹ With improvements in treatment methods, the long-term prognosis and quality of life of patients with a Fontan circulation is gaining importance.² However, the Fontan operation is rarely performed in children with Down syndrome³⁻⁶; therefore, the postoperative outcome for this group is not well known. Patients with Down syndrome are at risk of developing persistent pulmonary hypertension⁷ and airway obstruction,⁸ which may affect the outcome of univentricular repair. We report the result of total cavopulmonary connection (TCPC) performed in 8 children with Down syndrome.

METHODS

Patients

Between January 2004 and March 2010, 14 patients (11 boys and 3 girls) with Down syndrome among 240 total patients (120 boys and 120 girls) received a bidirectional superior cavopulmonary shunt

(BCPS), whereas 8 patients with Down syndrome (6 boys and 2 girls) among 235 patients (121 boys and 117 girls) underwent TCPC, excluding TCPC conversion or repeat TCPC, at Sakakibara Heart Institute. All patients underwent BCPS before TCPC during this period.

Clinical Protocol

We investigated children with Down syndrome who had undergone univentricular repair. In particular we took note of the clinical course after BCPS and patient characteristics, preoperative catheter data, surgical data, preoperative echocardiographic data, type of Fontan operation, postoperative data and clinical course, and lung biopsy results. Postoperative catheter data and mortality were evaluated after TCPC. Patient characteristics, including clinical diagnosis, sex, age at TCPC, and body weight at TCPC were also investigated. Preoperative catheter data, including oxygen saturation, mean pulmonary artery pressure, and Nakata's pulmonary artery index (PAI)⁹; and echocardiographic data, including aortic regurgitation and atrioventricular valve regurgitation, were graded as 0 = absent, 1 = trivial, 2 = mild, 3 = moderate, or 4 = severe. Postoperative data included central venous pressure (CVP) on entry into the intensive care unit (ICU), complications, index of pulmonary vascular disease,¹⁰ Heath-Edwards classification as derived from lung biopsy examination,¹¹ and postoperative oxygen saturation and CVP.

In addition, diagnostic category, preoperative catheter data, type of Fontan operation, postoperative data, clinical course, and mortality were compared between patients with Down syndrome (Down syndrome group, n = 8) and those without (non-Down syndrome group, n = 227). Postoperative data and clinical course were evaluated for the 2 groups with respect to the following parameters: CVP on entering the ICU, frequency of nitric oxide use, repeat surgery rate, duration of mechanical ventilation, duration of ICU stay, duration of pleural drainage, duration of hospital stay, and mortality. Mortality was categorized as either hospital death or late death (defined as death after discharge). We continued postoperative follow-up until December 2012. We evaluated all the above-mentioned parameters by performing a retrospective review of each patient's medical records.

From the Departments of Pediatrics,^a Juntendo University School of Medicine, Tokyo; and Departments of Pediatrics^b and Pediatric Cardiovascular Surgery,^c Sakakibara Heart Institute, Tokyo, Japan.

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Address for reprints: Takeshi Furukawa, Department of Pediatrics, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan (E-mail: furukawa.tks@gmail.com).

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FIGURE 1. Cavopulmonary shunt and cavopulmonary connection in children with Down syndrome. *BCPS*, Bidirectional superior cavopulmonary shunt; *TCPC*, total cavopulmonary connection.

Statistical Analyses

StatView version 5.0 software (SAS Institute, Inc, Cary, NC) was used for all statistical analyses. The data are expressed as mean $\pm$ standard deviation. Statistical significance was defined as $P < .05$. We used nonparametric tests to compare the parameters between the 2 groups. Differences in count or percentage data between the 2 groups were evaluated using χ^2 analysis with Yates correction for continuity.

RESULTS

The clinical course of patients with Down syndrome who received a BCPS is shown in Figure 1. Fourteen patients with Down syndrome received a BCPS, with no hospital deaths and 2 late deaths. One patient died a sudden death 4 months after BCPS, whereas the other died as a result of heart failure 29 months after BCPS. Eight patients underwent TCPC, and 4 patients are still awaiting TCPC.

In the 8 patients with Down syndrome who underwent TCPC, the median age at the time of TCPC was 4.1 years (range, 3.4–5.5 years) and the mean body weight was 13.1 kg (range, 9.6–15.0 kg). The preoperative mean pulmonary artery pressure was 13.9 ± 1.8 mm Hg, and PAI of all patients was above $200 \text{ mm}^2/\text{body surface area}$ (in meters²)

(Tables 1 and 2). We observed respiratory complications in 2 patients, surgical site infection in 3 patients, and chylothorax in 2 patients (Table 3). One patient (patient 2) died suddenly on postoperative day (POD) 17 because of a suspected pulmonary hypertension crisis. Results of lung biopsy obtained at autopsy revealed Heath–Edwards classification grade 3 and index of pulmonary vascular disease grade D. There were no late deaths in the other patients. One patient developed protein-losing enteropathy 8 months after TCPC.

As shown in Table 2, there was no significant difference in preoperative data and diagnostic category between the groups of children with and without Down syndrome. However, there was no case of hypoplastic left heart syndrome and heterotaxy syndrome in the Down syndrome group. Mortality was higher in the Down syndrome group (1 of 8 patients, 12.5%) than in the non-Down syndrome group (5 of 227 patients, 2.2%), although this difference was not statistically significant (Table 4). However, when the postoperative clinical course was examined, the rate of nitric oxide use (50.0% vs 7.9%; $P < .001$) and that of repeat surgery (25.0% vs 2.6%; $P = .015$) were higher in the Down syndrome group than in the non-Down syndrome group. Patient 6 underwent surgery for an enlarged fenestration at POD 1, whereas patient 7 underwent repeat TCPC at POD 4. Furthermore, the duration of mechanical ventilation (7.8 ± 6.9 days vs 2.6 ± 8.2 days; $P = .039$), duration of ICU stay (14.0 ± 9.9 days vs 5.2 ± 10.3 days; $P = .009$), duration of pleural drainage (17.0 ± 14.7 days vs 9.7 ± 10.3 days; $P = .027$), and duration of hospital stay (40.1 ± 31.3 days vs 27.7 ± 17.0 days; $P = .007$) were found to be significantly prolonged in the Down syndrome group (Table 4).

DISCUSSION

Our study showed that the incidence of mortality after TCPC was 2.2% in the non-Down syndrome group and 12.5% (1 of 8 patients) in the Down syndrome group,

TABLE 1. Characteristics and preoperative data of patients in the Down syndrome group

Patient	Diagnosis	Sex	Age, y	Weight, kg	SpO ₂ , %	Mean		AR, grade	AVVR, grade
						PAP, mm Hg	PAI, mm ² /m ²		
1	DORV, ASD, MS, Hypo-LV, CoA	Boy	4.8	13.2	81.9	15	274	0	2
2	uAVSD, Hypo-LV, CoA, LVOTO	Boy	2.4	9.6	80.1	11	305	0	2
3	SLV, CA, CoA	Boy	5.5	14.4	89.0	15	490	0	1
4	VSD, ASD(II), Straddling MV, Straddling TV	Boy	3.8	10.8	84.2	14	319	0	2
5	uAVSD, Hypo-RV	Boy	4.3	11.3	79.8	13	240	0	0
6	uAVSD, Hypo-RV	Boy	5.4	15.0	79.4	13	394	0	2
7	TOF, PA, uAVSD, Hypo-RV, PDA	Girl	3.4	13.0	76.6	13	251	1	2
8	cAVSD, CoA, LVOTO	Girl	3.8	14.7	74.0	17	447	1	1

SpO₂, Oxygen saturation; PAP, pulmonary artery pressure; PAI, pulmonary artery index; AR, aortic regurgitation; AVVR, atrioventricular valve regurgitation; DORV, double out right ventricle; ASD, atrial septal defect; MS, mitral stenosis; Hypo-LV, hypoplastic left ventricle; CoA, coarctation of aorta; uAVSD, unbalanced atrioventricular septal defect; LVOTO, left ventricular outflow tract obstruction; SLV, single left ventricle; MV, mitral valve; TV, tricuspid valve; Hypo-RV, hypoplastic right ventricle; TOF, tetralogy of Fallot; PA, pulmonary atresia; PDA, patent ductus arteriosus; CA, common atrium; VSD, ventricular septal defect.

TABLE 2. Comparison of preoperative data between groups of children with and without Down syndrome

	Down syndrome (n = 8)	No Down syndrome (n = 227)	P value
Boys, n (%)	6 (75)	115 (50.7)	.320
Median age at TCPC operation, y (range)	4.1 (34-5.5)	3.2 (1.0-45.5)	.143
Median weight, kg (range)	13.1 (9.6-15.0)	12.9 (6.7-69.1)	.136
Diagnostic categories, n (%)			
Function single LV	4 (50)	75 (33.0)	.537
Function single RV	2 (25)	52 (22.9)	.772
HLHS	0	20 (8.8)	.816
Heterotaxy syndrome	0	29 (12.7)	.594
Others	2 (25)	51 (22.5)	.793
Preoperative catheter			
CVP, mm Hg	7.43 ± 1.72	7.03 ± 2.57	.344
mPAP, mm Hg	13.9 ± 1.8	13.6 ± 3.0	.384
PAI	340.0 ± 93.2	282.3 ± 118.4	.087
AR	0.25 ± 0.46	0.20 ± 0.46	.388
AVVR	1.50 ± 0.76	0.98 ± 0.99	.071

TCPC, Total cavopulmonary connection; LV, left ventricle; RV, right ventricle; HLHS, hypoplastic left heart syndrome; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; PAI, pulmonary artery index; AR, aortic regurgitation; AVVR, atrioventricular valve regurgitation.

although there was no significant difference between the 2 groups. Gupta-Malhotra and colleagues³ studied 17 patients with Down syndrome who underwent TCPC and reported that mortality in the early period was 29% and significantly higher than that in patients without Down syndrome (10%).

They argued that Down syndrome itself is a strong independent factor of mortality. Our data indicate that there was no significant difference in preoperative data such as mean pulmonary artery pressure, PAI, aortic regurgitation, and atrioventricular valve regurgitation between the 2 groups, although the postoperative clinical course was prolonged significantly in the patients with Down syndrome. There were several patients in whom a serious postoperative clinical course was observed, and this could not be anticipated from the preoperative catheter data. Furthermore, the rates of nitric oxide use and repeat surgery were significantly high in the Down syndrome group in our study. One patient died suddenly as a result of a suspected pulmonary hypertension crisis, suggesting that it may be difficult to predict the outcome of TCPC on the basis of preoperative catheter data. Wada and colleagues⁵ reported the case of a patient who was awaiting Fontan surgery after BCPS. Although all criteria of TCPC had been fulfilled on the basis of preoperative hemodynamic studies, histologic analysis revealed hypertrophy of the tunica media in almost all preacinar small pulmonary arteries. Lung biopsy is an effective means of determining the outcome of TCPC in patients with Down syndrome.

Children with Down syndrome have a higher incidence of tracheal bronchus, abnormal segmental bronchial branching, laryngomalacia, and tracheomalacia.⁸ In our report, 2 of 8 patients developed respiratory tract disease as a complication, which was a reason for their long-term mechanical ventilation and prolonged ICU stay. There is evidence of a high incidence of chylothorax after Fontan

TABLE 3. Postoperative data of patients with Down syndrome

Patient	Type of operation	CVP, mm Hg	Complication	Respiration problem	Lung biopsy	Postoperative catheter		
						SpO ₂ , %	CVP, mm Hg	Outcome
1	Fenestrated extracardiac conduit	13	No	No	Pre-TCPC IPVD 1.0, HE 1	82.8	14	Alive (38 mo)
2	Extracardiac conduit	13	No	No	Autopsy IPVD 1.7, HE 3	Not done		Sudden death (POD 17)
3	Extracardiac conduit	18	SSI Chylothorax	Tracheostenosis	Not done	91.0	17	Alive (96 mo)
4	Fenestrated extracardiac conduit DKS, lung biopsy	11	No	No	At TCPC IPVD 1.0, HE 1	90.0	10	Alive (42 mo)
5	Extracardiac conduit	15	Chylothorax	No	Not done	94.0	14	Alive (85 months)
6	Fenestrated extracardiac conduit, PA plasty ⇒ Re-fenestration (POD 1)	15	SSI	No	Not done	Not done		Alive (27 mo)
7	Extracardiac conduit ⇒ TCPC repair (POD 4)	14	Thrombosis	No	Not done	92.0	12	Alive (19 mo)
8	Fenestrated extracardiac conduit	15	SSI PLE	Laryngomalacia Tracheal ring	Not done	94.5	11	Alive (19 mo)

CVP, Central venous pressure; SpO₂, oxygen saturation; Pre-TCPC, preoperative total cavopulmonary connection; IPVD, index of pulmonary vascular disease; HE, Heath-Edwards classification; POD, postoperative day; SSI, surgical site infection; DKS, Damus-Kaye-Stansel operation; PA, pulmonary artery plasty; TCPC, total cavopulmonary connection; PLE, protein losing enteropathy.

TABLE 4. Comparison of intraoperative and postoperative data for children with and without Down syndrome

	Down syndrome (n = 8)	No Down syndrome (n = 227)	P value
Fontan type			.031*
Extracardiac nonfenestrated	4 (50.0)	193 (85.0)	
Extracardiac fenestrated	4 (50.0)	34 (15.0)	
CVP after Fontan surgery	14.3 ± 2.1	13.7 ± 2.1	.217
Nitric oxide	4 (50.0)	18 (7.9)	<.001*
Repent surgery	2 (25.0)	6 (2.6)	.015*
Duration of mechanical ventilation, d	7.8 ± 6.9	2.6 ± 3.2	.039*
Duration of ICU stay, d	14.0 ± 9.9	5.2 ± 10.3	.009*
Duration of pleural drainage, d	17.0 ± 14.7	9.7 ± 10.3	.027*
Duration of hospital stay, d	40.1 ± 31.3	27.7 ± 17.0	.007*
Death	1 (12.5)	5 (2.2)	.500
Hospital death	1 (12.5)	4 (1.8)	
Late death	0	1 (0.4)	

Values are presented as n (%) or mean ± standard deviation. CVP, Central venous pressure; ICU, intensive care unit. *P < .05.

surgery in children with Down syndrome,⁶ with Campbell and colleagues⁴ reporting this complication in 3 of 4 patients. In our study, 2 of 8 patients developed chylothorax that tended to prolong the duration of pleural drainage. Furthermore, 3 patients (37.5%) developed surgical site infection. Down syndrome is associated with an increased frequency of infection, and several studies have reported immunologic dysfunction to be associated with Down syndrome.¹²⁻¹⁴ Abnormalities of the innate immune system and the prolonged duration of pleural drainage would be expected to predispose patients to surgical site infection and prolonged hospital stay.

In our study, only 8 patients with Down syndrome underwent TCPC, with the duration of follow-up being short. Various other complications are associated with Down syndrome, such as obstructive sleep apnea syndrome,¹⁵ obesity,¹⁶ recurrent lower respiratory tract infections, and gastroesophageal reflux.¹⁷ Approximately 50% of children with Down syndrome develop obstructive sleep apnea syndrome, which may contribute to the unexplained pulmonary hypertension associated with Down Syndrome.¹⁸ Gastroesophageal reflux, pulmonary aspiration, and lower respiratory tract infections also increase the risk of pulmonary hypertension in these patients,¹⁹ and it is possible that they contribute to the development of this complication after TCPC. A long-term follow-up study with a larger number of patients with Down syndrome is therefore required, and it is also necessary to further evaluate the outcome of TCPC in these patients.

Study Limitations

Ours was a retrospective study with a short follow-up duration. In addition, the number of patients with Down syndrome was only 8 and significantly lower than that of

patients without Down syndrome; this may have limited the results of the statistical evaluation of this study. Moreover, we made no mention of early palliative care in this investigation of univentricular repair.

CONCLUSIONS

We reported on 8 patients with Down syndrome who underwent TCPC. One of those 8 patients died after TCPC, whereas the clinical course and recovery after surgery in the other 7 patients was significantly prolonged. On the basis of these findings we consider it necessary to study more cases to evaluate mortality and long-term prognosis.

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