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Outcomes of Extracorporeal Membrane Oxygenation in Children: An 11-Year Single-Center Experience in Korea

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Background: Extracorporeal membrane oxygenation (ECMO) has become an important treatment modality in pediatric patients with cardiopulmonary failure, but few studies have been conducted in Korea. **Methods:** We conducted a retrospective review of pediatric patients younger than 18 years who were placed on ECMO between January 2004 and December 2014 at Samsung Medical Center. **Results:** We identified 116 children on ECMO support. The overall rate of successful weaning was 51.7%, and the survival to discharge rate was 37.1%. There were 39, 61, and 16 patients on ECMO for respiratory, cardiac, and extracorporeal cardiopulmonary resuscitation, respectively. The weaning rate in each group was 48.7%, 55.7%, and 43.8%, respectively. The survival rate was 43.6%, 36.1%, and 25.0%, respectively. Sixteen patients on ECMO had functional single ventricle physiology; in this group, the weaning rate was 43.8% and the survival rate was 31.3%. Ten patients were on ECMO as a bridge to transplantation (8 for heart and 2 for lung). In patients with heart transplantation, the rate of survival to transplantation was 50.0%, and the overall rate of survival to discharge was 37.5%. **Conclusion:** An increasing trend in pediatric ECMO utilization was observed. The outcomes were favorable considering the early experiences that were included in this study and the limited supply of specialized equipment for pediatric patients.

Key words: 1. Pediatric
2. Extracorporeal membrane oxygenation
3. Congenital heart disease
4. Transplantation
5. Heart-assist devices

Introduction

The first successful extracorporeal membrane oxygenation (ECMO) treatment was performed in a neonate with respiratory difficulty in 1976 by Bartlett et al. [1]. Since then, ECMO was primarily developed in the pediatric field, although its utilization has extended to adult patients [2-4]. Currently, ECMO is one of the most important treatment modalities worldwide for refractory pulmonary or cardiac failure not only in children, but also in adults [5].

In Korea, the first case of survival after ECMO was reported in 1991, in a 2-year-old patient with respiratory failure after a total correction of tetralogy of Fallot [6]. The number of applications of ECMO in adults has recently increased, and several studies re-

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garding ECMO in adults have been published [2,7,8]. Although several studies of ECMO have also been published in the pediatric field [9-12], published experiences and data regarding ECMO in Korea are limited. Since we acquired a peripheral ECMO device in 2004 [2], we have performed ECMO in children as well as in adults. In this study, we examined the outcomes of pediatric patients on ECMO between 2004 and 2014 at Samsung Medical Center.

Methods

We performed a retrospective review of 116 consecutive patients younger than 18 years old on ECMO between January 2004 and December 2014 at Samsung Medical Center, Seoul, Korea. In these patients, a total of 121 ECMO runs were performed. The size of the cannulas used for drainage ranged from 10 Fr to 28 Fr based on the age, weight, and size of the patients, and that of the perfusion cannulas ranged from 8 Fr to 21 Fr. The specific cannulation strategy based on the patients' age is presented in Table 1.

In cases of femoral artery cannulation in small children, we preferred to use a short segment of a vascular graft (Gore-Tex Stretch Vascular Graft; W. L. Gore & Associates, Flagstaff, AZ, USA) anastomosed to the common femoral artery in an end-to-side fashion. The diameter of the graft (5 or 6 mm) was determined according to the arterial size of the patient. Insertion of a distal perfusion catheter was considered in older children if a perfusion cannula larger than 15 Fr was needed, or if there was evidence of limb ischemia.

We used 3 kinds of ECMO pumps: Bio-Pump (Medtronic, Minneapolis, MN, USA), Emergency Bypass System (Terumo Inc., Tokyo, Japan), and Rotaflow (Maquet, Rastatt, Germany). In addition, 3 kinds of membrane oxygenators were used: the Emergency Bypass System, Quadrox (Maquet, Rastatt, Germany), and Lilliput 2 ECMO (Sorin, Munich, Germany). During ECMO support, unfractionated heparin was continuously infused for anticoagulation to achieve an activated clotting time between 150 and 200 seconds.

Relevant clinical variables were collected at the initiation of and during ECMO support. Overall outcomes including the successful weaning rate and the survival to discharge rate were calculated. Successful

Table 1. Cannulation strategy for pediatric ECMO

Variable	VA ECMO[a]				VV ECMO[a]		
	Drain site	Perfusion site	Cannulation method	Carotid ligation	Drain site	Perfusion site	Cannulation method
Neonate	RIJV	RCCA	Open	+	RIJV (DLC 12 Fr or 15 Fr)		Open (preferred) or percutaneous
Infant			Open or semi-open	+/-	RIJV (DLC 15 Fr)		Percutaneous (preferred) or semi-open
Toddler			Semi-open (preferred) or open	-	RIJV (DLC 15 Fr) (preferred) or separate cannulation		
Child	FV	Vascular graft attached to FA	Semi-open (preferred) or open		FV	RIJV	
Adolescent		FA[b] (+distal perfusion)	Percutaneous				Percutaneous

ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous; RIJV, right internal jugular vein; RCCA, right common carotid artery; DLC, double lumen cannula; FV, femoral vein; FA, femoral artery.
[a]Always consider central cannulation if the flow is not satisfactory, especially in small children, or if the patient is on early poststernotomy status. [b]A cannula larger than 15 Fr without distal perfusion should be avoided.

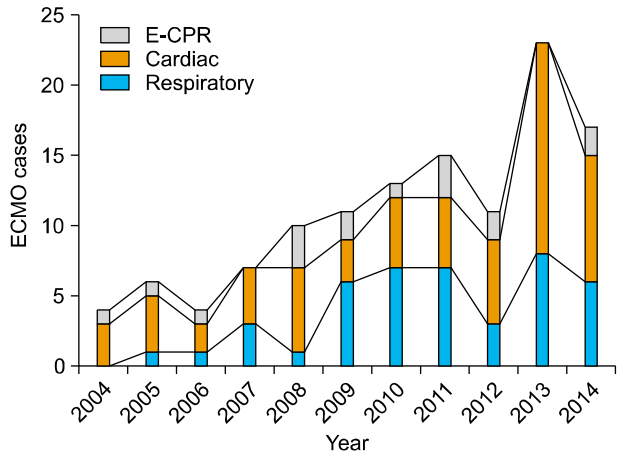

Fig. 1. Pediatric ECMO cases by year. ECMO, extracorporeal membrane oxygenation; E-CPR, extracorporeal cardiopulmonary resuscitation.

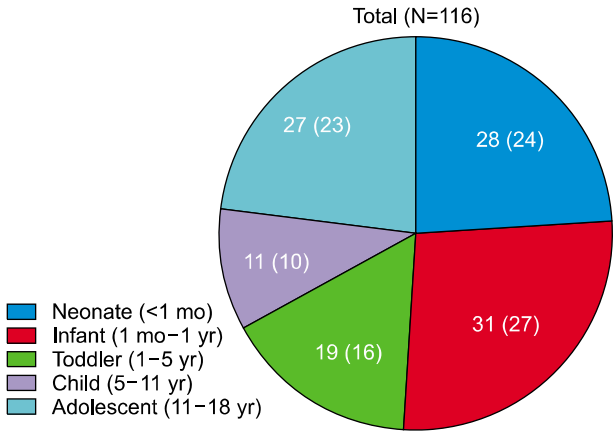

Fig. 2. Age distribution of pediatric ECMO. ECMO, extracorporeal membrane oxygenation. Values are presented as number (%).

weaning was defined as weaning without reinsertion of ECMO or death within 24 hours. If a patient underwent 2 or more separate ECMO runs, only the first run of ECMO was analyzed to calculate the outcomes. Complications during ECMO were categorized as follows: (1) bleeding (cannulation or surgical site bleeding requiring an intervention); (2) brain injury (clinical or electroencephalographic seizures, central nervous system hemorrhage, or infarction causing diffuse ischemic injury); (3) limb ischemia (pain, pallor, mottling, or evidence on a duplex scan); (4) a mechanical complication requiring circuit change (oxygenator failure, pump failure, air in circuits, or tube rupture). Further, we reviewed the number of circuit changes during ECMO. Thereafter, we calculated the outcomes of the subgroups such as respiratory failure, cardiac failure, and extracorporeal cardiopulmonary resuscitations (E-CPR), neonates, pediatric patients, patients with functional single ventricle physiology, and patients in whom ECMO was used for a bridge to heart transplantation. We compared the outcomes of the early era (2004–2009) with that of the later era (2010–2014). In patients who underwent cardiac ECMO, the outcomes of patients with congenital heart disease (CHD) were compared with those of patients without CHD. Continuous variables are presented using median and range, and categorical variables were compared using the chi-square test.

Results

The annual number of pediatric ECMO cases is shown in Fig. 1, and the age distribution is shown in Fig. 2. The patient demographics are presented in Table 2. Overall, 63 male patients (54.3%) and 53 female patients (45.7%) were on ECMO. Their median age was 11 months (range, 1 day to 17 years), and their median body weight was 8.22 kg (range, 2.0 to 88.2 kg). In addition, 72.4% (84 of 116) of the patients were on venoarterial ECMO, while 27.6% (32 of 116) were on venovenous ECMO. Among the patients with respiratory failure, cardiac failure, and E-CPR, 39, 61, and 16 were on ECMO, respectively. The median duration of ECMO in all patients was 6.0 days (range, 3.0 to 12.8 days). Altogether, 51.7% (60 of 116) of the patients were successfully weaned from ECMO and the survival to discharge rate for all patients was 37.1% (43 of 116). Comparing cohorts from 2004–2009 (n=41) to 2010–2014 (n=75), the successful weaning rate (early era 41.5% versus late era 57.3%, p=0.102) and the survival to discharge rate (early era 26.8% versus late era 42.7%, p=0.091) were not significantly different. There were 33 cases (28.4%) of bleeding, 16 (13.8%) of brain injury, and 5 (4.3%) of limb ischemia. Forty-nine patients (42.2%) needed one or more circuit change.

Comparing patients who underwent cardiac ECMO with and without CHD, the survival outcome was worse in patients with CHD (with CHD 23.7% versus without CHD 56.5%; odds ratio, 0.24; p=0.01).

Table 2. Overall outcomes of ECMO

Variable	Overall (N=116)	Respiratory (N=39)	Cardiac (N=61)	E-CPR (N=16)
Age	11 mo (1 day–17 yr)	10 mo (2 day–17 yr)	7 mo (2 day–17 yr)	6.5 yr (1 day–17 yr)
Body weight (kg)	8.2 (2.0–88.2)	8.3 (2.0–61.3)	7.4 (2.1 – 88.2)	19.7 (3.1–71.1)
Male sex	63 (54.3)	18 (46.2)	34 (55.7)	11 (68.8)
Duration of ECMO	6.0 day (30 min–135 day)	6.0 day (3 hr–135 day)	6.0 day (6 hr–58 day)	2.0 day (30 min–17 day)
Successful weaning	60 (51.7)	19 (48.7)	34 (55.7)	7 (43.8)
Survival to discharge	43 (37.1)	17 (43.6)	22 (36.1)	4 (25.0)

Values are presented as mean (range) or number (%), unless otherwise stated.
ECMO, extracorporeal membrane oxygenation; E-CPR, extracorporeal cardiopulmonary resuscitation.

Table 3. The underlying diagnoses and outcomes of extracorporeal membrane oxygenation in neonates

Diagnosis	No. of cases	No. of survivors	Survival (%)
Neonatal respiratory	14	4	28.6
Congenital diaphragmatic hernia	5	1	20.0
Meconium aspiration syndrome	3	3	100.0
Persistent pulmonary hypertension	3	0	0
Respiratory distress syndrome	2	0	0
Sepsis	1	0	0
Neonatal cardiac	12	3	25.0
Preoperative stabilization	1	0	0
Cardiopulmonary bypass weaning failure	6	3	50.0
Postoperative low cardiac output syndrome	5	0	0
Neonatal extracorporeal cardiopulmonary resuscitation	2	1	50.0

1) Neonatal patients

ECMO was performed in 28 neonatal patients (i.e., ≤30 days at the time of ECMO initiation). Their median age was 4.5 days (range, 1.0 to 25.0 days), and their median body weight was 3.0 kg (range, 2.0 to 3.9 kg). Overall, ECMO was performed in 14, 12, and 2 neonates with respiratory failure, cardiac failure, and E-CPR, respectively. The survival to discharge rate in these patients was 28.6%, 25%, and 50%, respectively. Among the neonates with cardiac failure, ECMO support was performed in 1 case for preoperative stabilization of a patient with total anomalous pulmonary venous return and pulmonary hypertension. The underlying diagnoses of the neonatal patients on ECMO support are documented in Table 3. In the neonatal respiratory ECMO patients, the median time between the onset of an oxygenation index (OI) greater than 40 and the initiation of ECMO was 16.1 hours (range, 3.2 to 35.3 hours), and all patients required inotropic support when ECMO was initiated.

2) Pediatric patients

ECMO was performed in 88 pediatric patients. Their median age was 2.5 years (range, 0.1 to 17.0 years), and their median body weight was 13.1 kg (range, 2.7 to 88.2 kg). Overall, ECMO was performed in 25, 49, and 14 pediatric patients with respiratory failure, cardiac failure, and E-CPR, respectively. The survival to discharge rate in these patients was 52.0%, 40.8%, and 21.4%, respectively. Among the children with cardiac failure, in 2 cases, ECMO support was performed for preoperative stabilization, in one patient with a postoperative pulmonary venous stenosis and in another patient who underwent reoperation after total correction of a left pulmonary artery sling. The underlying diagnoses in this patient population are shown in Table 4.

3) Functional single ventricle

Sixteen patients with functional single ventricle physiology were on ECMO. Their median age was 4.5 months (range, 7 days to 15 years) and their median body weight was 5.9 kg (range, 2.7 to 40.2 kg). The

Table 4. The underlying diagnoses and outcomes of extracorporeal membrane oxygenation in pediatric patients

Diagnosis	No. of cases	No. of survivors	Survival (%)
Pediatric respiratory	25	13	52.0
Trauma	2	2	100.0
Interstitial lung disease	4	0	0
Airway obstruction	5	3	60.0
Pneumonia, all-cause	14	8	57.1
Pediatric cardiac	49	20	40.8
CHD-related	26	6	23.1
Preoperative stabilization	2	0	0
Cardiopulmonary bypass weaning failure	15	3	20.0
Postoperative low cardiac output syndrome	9	3	33.3
Non-CHD related	23	13	56.5
Myocarditis	11	6	54.5
Cardiomyopathy	7	3	42.9
Intractable arrhythmia	3	3	100
Pulmonary hypertension	2	1	50.0
Pediatric extracorporeal cardiopulmonary resuscitation	14	3	21.4

CHD, congenital heart disease.

median duration of ECMO support was 7.5 days (range, 3.0 to 27 days). Overall, 43.8% (7 of 16) of the patients were successfully weaned from ECMO, and 31.3% (5 of 16) survived to discharge. ECMO for patients with functional single ventricle was performed in 11 and 5 pediatric patients after stage 1 palliative procedures and Glenn procedures, respectively. In our study population, there were no ECMO cases after the Fontan procedure, excluding 1 patient older than 18 years old. Among the 11 patients on ECMO after stage 1 procedures, 7 needed ECMO support for failed weaning from cardiopulmonary bypass, 2 for postoperative low cardiac output syndrome, 1 for E-CPR, and 1 for respiratory failure due to alveolar hemorrhage. Further, among the 5 patients who underwent ECMO after a Glenn procedure, 3 patients needed ECMO support for failed weaning from cardiopulmonary bypass, 1 for E-CPR, and 1 for respiratory failure due to viral pneumonia. The successful weaning rate in patients in single ventricle was 54.5% (6 of 11) after stage 1 procedures and 20% (1 of 5) after Glenn procedures. The survival to discharge rate was 36.4% (4 of 11) after stage 1 procedures and 20% (1 of 5) after Glenn procedures.

4) Transplantation or left ventricular assist device

During ECMO support, 8 patients were on the waiting list for heart transplantation, and 2 patients for lung transplantation. The characteristics of the patients on the list for heart transplantation are shown in Table 5. Among them, 5 were successfully weaned from ECMO before the heart transplant or transition to an extracorporeal left ventricular assist device (E-LVAD). Three patients (#1, #2, and #5) had heart transplantations while on ECMO support. In another patient (#3), ECMO was transitioned to E-LVAD on the 10th day, and the patient received the heart transplantation on the 48th day of E-LVAD with 2 circuit changes. In the other patient (#4), we changed the circuit to E-LVAD on the 13th day, but the patient died from an intracranial hemorrhage while still on the waiting list. He died on the 130th day of E-LVAD and needed a single circuit change. After heart transplantation, there was 1 additional mortality from pulmonary hemorrhage and septic shock (#1). The application of E-LVAD as a bridge to transplantation has started recently, although it was only performed for long-term support in patients with good right ventricular and pulmonary function. However, 1 of the 2 patients on the list for lung transplantation died from right ventricular dysfunction after 135 days of ECMO support. The other patient underwent bilateral pulmonary transplantation on the 44th day of ECMO. However, he could not be weaned from ECMO and died from refractory pulmonary failure on the 123rd day of ECMO.

Table 5. The characteristics of patients with ECMO on the list for heart transplantation

Case	Sex	Age	Body weight (kg)	Diagnosis	ECMO duration (day)	Successful ECMO weaning	Survival to discharge	Cause of death
1	M	2 yr	12.7	DCMP	23	Yes (heart transplantation)	No	Pulmonary hemorrhage, septic shock
2	F	3 yr	12.3	DCMP	19	Yes (heart transplantation)	Yes	
3	F	5 yr	18	DCMP	10	Yes (E-LVAD→eart transplantation)	Yes	
4	M	11 yr	26	DCMP	13	Yes (E-LVAD)	No	Brain hemorrhage
5	M	15 yr	36.8	Rejection after heart transplantation due to DCMP	58	Yes (redo heart transplantation)	Yes	
6	M	3 mo	4.8	DCMP, ASD	63	No	No	DIC, MOF
7	F	4 mo	5.2	Fulminant myocarditis	30	No	No	MOF
8	F	10 yr	23.7	Lupus myocarditis	17	No	No	Respiratory failure MOF

ECMO, extracorporeal membrane oxygenation; M, male; F, female; DCMP, dilated cardiomyopathy; E-LVAD, extracorporeal left ventricular assist device; ASD, atrial septal defect DIC, disseminated intravascular coagulation; MOF, multiorgan failure.

Discussion

ECMO has recently become one of the most important resuscitative methods in patients with cardiovascular failure or pulmonary collapse. We observed that the number of pediatric cases on ECMO increased every year at our institution. With the increasing number of ECMO cases, our ECMO team has accumulated experience. Our recent outcomes, although seemingly statistically insignificant compared with those of earlier periods, have shown a trend for improvement. In Korea, most published reports of pediatric patients on ECMO have described a small number of cases, and there is a lack of collective data regarding these patient populations. To our knowledge, the present study is the first collective review of pediatric ECMO cases with a relatively large number of patients in Korea.

In our study, the overall survival rate in neonates with respiratory failure on ECMO was 28.6%, which is somewhat unsatisfactory at first glance. In Korea, the reason for these unsatisfactory results might include the lack of proper neonatal equipment, inappropriate patient selection, and delayed ECMO application. In particular, there has been a shortage of ECMO equipment optimized for pediatric patients, including double-lumen cannulas, pediatric oxygenators, and pediatric pumps. The neonatal use of ECMO circuits optimized for adults might cause a number of problems, such as large priming volume, a low flow rate, and consequent thrombosis and failure of the oxygenator. Therefore, frequent circuit changes were inevitable, and every circuit change has the potential to harm the patient. In Korea, unlike Western countries, ECMO is generally introduced after other neonatal respiratory modalities, such as high-frequency oscillating ventilators, surfactants, and inhaled nitric oxide. Because of this, ECMO is still considered as the last option by many neonatologists, and therefore, timely ECMO initiation does not always take place. The OI is the most commonly utilized criterion for neonatal respiratory ECMO, and ECMO initiation after 3 hours with an OI >40 is an adverse prognostic factor [13]. In our study, the median time from OI >40 to ECMO was 16.1 hours (range, 3.2 to 35.3 hours), and all patients required inotropic support at the initiation of ECMO. ECMO was considered as the last option after the use of other modalities and after significant progression of cardiopulmonary dysfunction, which may have had an adverse effect on the prognosis. Considering the limited resources and the circumstances in Korea, our outcomes of neonatal respiratory ECMO seem acceptable, although it is necessary to improve outcomes by introducing proper neonatal equipment, patient selection, and timely support.

In our study, the survival rate of pediatric patients with respiratory failure on ECMO was 52.0%, which is comparable to that of the Extracorporeal Life Support Organization (ELSO) registry (57%) [5]. The

most common diagnosis in this group was pneumonia (14 of 25), including bacterial and viral etiologies. Ji et al. [10] reported successful treatment with ECMO of a 3-year-old girl with acute respiratory distress syndrome and necrotizing pneumonia from an H1N1 influenza viral infection during the 2009 H1N1 influenza epidemic. In another report, Choi et al. [9] reported early success rates in pediatric patients with respiratory failure on venovenous ECMO using double-lumen cannulas. In our study, we used double-lumen cannulas in 22 small children with respiratory failure on venovenous ECMO. Although we lacked supplies and could only use 12 Fr and 15 Fr cannulas, we were able to avoid additional venous cannulations or central cannulations in these small children.

Thourani et al. [14] performed a study of 27 children with cardiac failure on venoarterial ECMO and found that the in-hospital survival rate of patients on non-resuscitative and resuscitative ECMO was 41.7% (5 of 12) and 73.3% (11 of 15), respectively (p= 0.130). The cumulative hospital survival rate in previously published studies of this patient population was 45% (788 of 1,755) [15]. In our study, the survival to discharge rate in these patients on ECMO and E-CPR was 35.9% and 23.5%, respectively. The survival outcomes of pediatric patients with cardiac failure on ECMO in our study are comparable to those of previously reported studies. Thourani et al. [14] reported an in-hospital survival rate of 88% in a group of patients with cardiomyopathy-myocarditis-arrhythmia, which is not related to CHD. In our study, the survival rate of patients with CHD was 23.7% (9 of 38). Patients without CHD had better outcomes (56.5%, 13 of 23; odds ratio, 0.24; p=0.01).

Previous studies have reported survival outcomes after ECMO in patients with a shunted single ventricle, and patients after Glenn or Fontan operations. Joffe et al. [15] analyzed previous studies of patients with a shunted single ventricle on ECMO and reported a cumulative hospital survival rate of 44% (71 of 162), ranging in individual reports from 17% to 50% [16,17]. Meanwhile, a few published studies reported a poor survival rate for ECMO in patients who underwent Glenn (17%) or Fontan (44%) operations [15]. In our study, the survival to discharge rate in patients after stage I palliative procedures was 36.4% (4 of 11). Of the 5 patients on ECMO after Glenn procedures, 1 (20.0%) patient survived to discharge. In the management of the patients with system-to-pulmonary shunts during ECMO, we used to clip the shunt in early days. However, in most of these cases, the sternal wound remained open with central cannulation. Thus, during ECMO support in patients with good pulmonary function, we have recently come to prefer leaving the shunt open and to removing the oxygenator, similar to a ventricular assist device (VAD).

In our study, we evaluated the survival to heart transplantation rate and the overall survival to discharge rate in 8 children on ECMO as a bridge to heart transplantation, and found rates of 50.0% (4 of 8) and 37.5% (3 of 8), respectively. These results are comparable to the outcomes of a previously published study (45% for survival to transplantation and 47% for survival to discharge) [18]. In 2011, Merrill et al. [19] reviewed 777 patients who were part of the ELSO registry, and found that prolonged ECMO support (i.e., uninterrupted ECMO for $\geq$14 days) in children was associated with poor survival. However, in cases of ECMO as a bridge to heart transplantation in adult patients, Cho et al. [7] suggested that a scoring system such as the model for end-stage liver disease score modified by the United Network for Organ Sharing may be an independent predictor distinct from the duration of ECMO. ECMO duration probably has a greater impact on outcomes in children than in adults because of the lack of equipment optimized for children and children's vulnerability to ECMO-related complications, including bleeding and hemolysis. Merrill et al. [19] demonstrated that using prolonged ECMO in children with cardiac failure is not ideal, and instead suggested that children should be transitioned to more viable types of cardiac support, such as a VAD, within the first few days of ECMO support. Fraser et al. [20] conducted a prospective single-group trial to compare the use of ECMO and VAD as a bridge to heart transplantation in 48 children, and reported superior survival rates in patients with VAD, compared with those in patients with ECMO. In addition, Weinstein et al. [21] reviewed 26 cases of VAD as a bridge to heart transplantation in children with single ventricle physiology, and reported that VAD had an overall success rate of 42%, which was higher than that of ECMO (33%). However, no implantable or paracorporeal VAD product has yet been

approved for children in Korea. Despite our lack of options, we performed a case of heart transplantation safely after up to 58 days of ECMO support. In our institution, after the accumulation of experience with ECMO support, we sought to develop a more durable system, and in 2 cases, we were able to transform an ECMO system into an E-LVAD system by removing the oxygenator, which is less durable and is one of the major sources of complications. The E-LVAD transformation was performed only in patients with good right ventricular and pulmonary function. Our recent strategy for E-LVAD application is to transform the ECMO system into an E-LVAD system within 2 weeks from the initiation of ECMO, or to initiate an E-LVAD directly in an elective setting.

In conclusion, this study, which is the first collective review of pediatric ECMO in Korea to our knowledge, shows an increasing trend in pediatric ECMO use, and the outcomes seem acceptable considering the limited resources available in Korea. However, to improve outcomes, devices optimized for children, including VADs, oxygenators, and double-lumen cannulas, urgently need to be introduced. In particular, the prompt adoption of paracorporeal or durable implantable VADs should be considered to improve the outcomes of patients requiring long-term cardiac support. Proper patient selection and timely support is also required for improvements to be made.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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