Results of Extracorporeal Cardiopulmonary Resuscitation in Children

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Background: Survival of children experiencing cardiac arrest refractory to conventional cardiopulmonary resuscitation (CPR) is very poor. We sought to examine current era outcomes of extracorporeal CPR (ECPR) support for refractory arrest. **Methods:** Patients who were ＜18 years and underwent ECPR between November 2013 and January 2016 were including in this study. We retrospectively investigated patient medical records. **Results:** Twelve children, median age 6.6 months (range, 1 day to 11.7 years), required ECPR. patients' diseases spanned several categories: congenital heart disease (n=5), myocarditis (n=2), respiratory failure (n=2), septic shock (n=1), trauma (n=1), and post-cardiotomy arrest (n=1). Cannulation sites included the neck (n=8), chest (n=3), and neck to chest conversion (n=1). Median duration of extracorporeal membrane oxygenation was five days (range, 0 to 14 days). Extracorporeal membrane oxygenation was successfully discontinued in 10 (83.3%) patients. Nine patients (75%) survived more than seven days after support discontinuation and four patients (33.3%) survived and were discharged. Causes of death included ischemic brain injury (n=4), sepsis (n=3), and gastrointestinal bleeding (n=1). **Conclusion:** ECPR plays a valuable role in children experiencing refractory cardiac arrest. The weaning rate is acceptable; however, survival is related to other organ dysfunction and the severity of ischemic brain injury. ECPR prior to the emergence of end-organ injury and prevention of neurologic injury might enhance survival.

Key words: 1. Extracorporeal cardiopulmonary resuscitation
2. Child
3. Cardiopulmonary bypass
4. Resuscitation

INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) is the simultaneous deployment of extracorporeal membrane oxygenation (ECMO) and CPR to provide immediate cardiovascular support for patients who are experiencing cardiac arrest unresponsive to conventional CPR. Several reports in recent years have demonstrated the advantage of ECPR in rescuing children unresponsive to CPR, with survival rates between 33% and 56% [1-7]. However, evidence from four observational studies of pediatric in-hospital cardiac arrest (IHCA) has shown no overall benefit to the use of ECPR compared to CPR without ECMO [8-11]. In 2015, the American Heart Association recommended ECPR for consideration in pediatric patients with cardiac diagnoses who have IHCA in the setting of existing ECMO protocols, expertise, and equipment [12]. Therefore,

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Table 1. Characteristics of 12 pediatric patients who underwent extracorporeal CPR

Patient	Age	Body weight (kg)	Sex	Diagnosis	Location	Cannulation site	CPR time (min)	Cannulation time (min)	ECMO time of day	ECMO uration (day)	Weaning	Survival >7	Survival until discharge
1	5.6 yr	11.4	M	CHD (single ventricle)	GW→HICU	Neck	66.0	18.0	Day	14	Yes	Yes	No
2	22 day	3.6	M	Post-cardiotomy (single ventricle)	HICU	Chest	58.0	23.0	Night	5	Yes	Yes	No
3	6.7 mo	8.9	F	Myocarditis	HICU	Neck	10.0	58.0	Night	2	Yes	Yes	Yes
4	6.5 mo	8.6	F	Respiratory failure	ICU	Neck	86.0	42.0	Day	3	Yes	Yes	Yes
5	4.5 mo	5.1	F	Respiratory failure	PCCU→HICU	Neck	61.0	32.0	Day	5	Yes	Yes	No
6	11.7 yr	31.0	F	Myocarditis	HICU	Neck	13.0	32.0	Day	6	Yes	Yes	Yes
7	1 day	2.6	M	CHD	NICU	Chest	44.0	30.0	Day	5	Yes	Yes	No
8	6.3 yr	26.0	M	Trauma	ER→ICU	Neck	75.0	69.0	Day	0	No	No	No
9	20.1 mo	11.0	F	Septic shock	ICU	Neck→chest	94.0	78.0	Day	6	No	No	No
10	3.8 mo	8.7	F	CHD	ER→HICU	Neck	61.0	27.0	Day	5	Yes	No	No
11	5.6 mo	6.5	M	CHD (single ventricle)	PCCU	Neck	67.0	37.0	Day	6	Yes	Yes	No
12	9.5 yr	24.6	M	CHD	GW→HICU	Chest	62.0	28.0	Day	2	Yes	Yes	Yes

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; M, male; CHD, congenital heart disease; GW, general ward; HICU, heart intensive care unit; F, female; ICU, intensive care unit; PCCU, pediatric critical care unit; NICU, neonatal intensive care unit; ER, emergency room.

we sought to examine current era outcomes of ECPR support for refractory arrest at Severance Cardiovascular Hospital.

METHODS

From November 2013 to January 2016, 12 children underwent ECPR at Severance Cardiovascular Hospital. We retrospectively reviewed the medical records of pediatric patients. Patient characteristics are summarized in Table 1. Patients were diagnosed as follows: congenital heart disease (n=5), myocarditis (n=2), respiratory failure (n=2), septic shock (n=1), trauma (n=1), and post-cardiotomy arrest (n=1). The median age was 6.6 months (range, 1 day to 11.7 years), and the median body weight was 9 kg (range, 2.6 to 31 kg). Four of the five congenital heart disease cases (patients 1, 7, 10, and 11) were untreated or had residual lesions. Another patient (patient 12) had sudden cardiac arrest due to coronary artery thrombotic obstruction seven days after aortic valve replacement. ECPR was indicated in children who did not respond to conventional CPR and those with disease or injury expected to be reversible. Patients who were in a hemodynamically unstable condition and placed on ECMO urgently without active cardiac arrest were not included in this study.

1) Extracorporeal membrane oxygenation technique and management

All patients were supported with venoarterial ECMO. ECMO was set up in the intensive care unit (ICU). If the arrest happened in the emergency room or general ward, then the patient was transferred to the ICU and the ECMO procedure was begun. The vascular approach used for cannula insertion was via peripheral access, and the route used was through the right neck using the right internal carotid artery and the right internal jugular vein when children had no perioperative sternotomy (i.e., cardiotomy within two weeks). Those who had a perioperative sternotomy or opened sternum were cannulated through the chest. The appropriate cannula size was determined by the surgeon's direct measurement.

Cannulation sites included the neck (n=8), chest (n=3), and neck to chest conversion (n=1). Patient 9 underwent cannulation conversion from the neck to the chest because the right internal jugular vein was difficult to approach after removal

of a continuous renal replacement catheter. We attempted to cannulate through the neck vessel first; however, bleeding and collapse of the right internal jugular vein with interruption of continuous cardiac massage made this difficult.

Patients were administered a loading dose of heparin (50 U/kg) 3 to 5 minutes before cannulation. Patients were maintained on a continuous intravenous heparin infusion to achieve an activated clotting time between 160 and 180 seconds. The goal for the activated clotting time was adjusted if there were issues with bleeding or coagulation, which included an oxygenator thrombus or left ventricular thrombus. Because of the lack of prompt, freely available perfusionists, we used pre-assembled, simplified, and commercialized ECMO systems: nine patients received the Capiox EBS (Terumo Ltd., Tokyo, Japan) and three patients received the Quadrox PLS (MAQUET Cardiovascular, Hirlingen, Germany).

The median CPR duration was 61.5 minutes (range, 10 to 94 minutes). The median cannulation time was 32 minutes (range, 18 to 78 minutes). ECMO was set up on a weekday between 7:00 AM and 7:00 PM in 10 of the 12 patients.

After starting ECMO, delivery of the inotropic agent was diminished with close observation of pulse pressure. Generally, 0.5 μg/kg・min milrinone was used, and the ECMO flow was adjusted with close monitoring of the echocardiogram, pulse pressure, arterial blood gas analysis, and chest X-ray. Sedation was maintained using intravenous midazolam, fentanyl, and ketamine. Muscle relaxants were not routinely used because they interfere with the determination of neurological changes. Diuretics were administered to achieve a negative fluid balance. If acute renal failure developed, continuous renal replacement therapy was initiated by connecting to the ECMO circuit instead of creating a separate route to prevent bleeding complications. All inflow and outflow lines were connected to the venous drainage line to prevent an air embolism. Assessment of the underlying cause leading to cardiac arrest was begun soon after patient stabilization, and further intervention was considered to address and treat the underlying cause and optimize the patient for future weaning.

In patients who had cardiac arrest, follow-up echocardiography was conducted up to every 12 hours to evaluate the recovery of the heart, detect residual lesions and thrombus formation in the ventricle, and to assess the need for heart trans-

plantation in case of failure of heart recovery. The decision to wean the patient from ECMO was determined by mutual agreement of the surgeon and physicians, including the cardiologist and pulmonologist, during a daily meeting. Weaning was initiated when the left ventricular ejection fraction improved more than 30% and there was no hemodynamic change after temporary cessation of ECMO flow for 5 to 10 minutes. ECMO weaning was performed concurrent with increased administration of inotropic drugs and heparin to prevent thrombosis.

This study was approved by the institutional review board at Yonsei University Health System, with a waiver of the need to obtain consent granted for this retrospective study (4-2015-1028).

2) Statistical analyses

Descriptive statistics reported include the median, range for continuous variables, and frequencies and percentages for categorical variables. Unrelated two-group comparisons were performed using unpaired, two-tailed t-tests or the Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Data were analyzed using IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA). All statistical tests were two-sided and significance was defined as $p < 0.05$.

RESULTS

The median duration of ECMO support was 5 days (range, 0 to 14 days). ECMO was successfully discontinued in 10 patients (83.3%). Patient 12, who had a coronary artery thrombotic obstruction seven days after aortic valve replacement, received a heart transplantation successfully.

Nine patients (75%) survived more than seven days after support discontinuation, and four patients (33.3%) survived and were discharged. Causes of death included ischemic brain injury (n=4), sepsis (n=3), and uncontrolled gastrointestinal bleeding (n=1).

We compared variables between surviving patients and non-surviving patients (Table 2). Surviving patients were significantly older than non-surviving patients (p=0.048), but there was no significant difference in other variables including the cannulation site, ECMO time, CPR time, cannulation

Table 2. Comparative data between surviving patients and non-surviving patients

Variable	Survivor (n=4)	Non-survivor (n=8)	p-value
Age (mo)	60.5 (range, 6.5–140.1)	5.1 (range, 0–76.0)	0.048
Weight (kg)	16.8 (range, 8.6–31.0)	7.6 (range, 2.6–26.0)	0.129
Sex			0.545
Male	1 (25.0)	5 (62.5)	
Female	3 (75.0)	3 (37.5)	
Extracorporeal CPR location			0.999
Heart ICU	3 (75.0)	5 (62.5)	
Other ICU	1 (25.0)	3 (37.5)	
Cannulation site			0.999
Neck	3 (75.0)	5 (62.5)	
Central	1 (25.0)	3 (37.5)	
ECMO time			0.999
Weekday	3 (75.0)	7 (87.5)	
Weeknight	1 (25.0)	1 (12.5)	
Perioperative period	1 (25.0)	2 (25.0)	0.999
CPR time (min)	37.5 (range, 10–86)	63.5 (range, 44–94)	0.461
Cannulation time (min)	37 (range, 28–58)	31 (range, 18–78)	0.952
ECMO duration (hr)	66.5 (range, 55–166)	133.5 (range, 2–336)	0.275
Diagnosis			
Single ventricle	0	3 (37.5)	0.491
Myocarditis	2 (50.0)	0	0.091

Values are presented as median (range) or number (%).
CPR, cardiopulmonary resuscitation; ICU, intensive care unit ECMO, extracorporeal membrane oxygenation.

time, duration of ECMO support, and diagnosis.

We also compared these variables between patients for whom ECMO weaning was successful and those for whom it failed (Table 3). The cannulation time was significantly shorter in the successful cases than in the failures (p=0.001). However, the other variables, including age, cannulation site, ECMO time, CPR time, duration of ECMO support, and diagnosis, did not differ significantly between the two groups.

DISCUSSION

In children, the survival rate after cardiac arrest is reportedly 9% to 47% for in-hospital events and 0% to 29% for events outside the hospital [4,6,13-15]. In comparison, the survival rate for pediatric ECPR is between 33% and 56% [1-7]. However, according to the American Heart Association recommendation in 2015, ECPR can be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment

[12]. If the child experiences cardiac arrest outside the hospital, ECPR cannot be performed easily even if the child is promptly transferred to the nearest hospital. Unlike those of adults, the femoral vessels of children are small; therefore, it is very difficult to perform a percutaneous cannulation of a very small collapsed vessel. Furthermore, if the procedure is to be performed via a neck vessel, an experienced cardiac surgeon should perform it; however, excluding large hospitals which have good congenital heart surgery programs with skilled professionals available at all times, the ECMO procedure for a collapsed vessel in a child cannot be performed smoothly with available staff. Even though the arrest may happen inside the hospital, if a child is in the bed of a general ward without an arterial or central line, the ECMO procedure is not easy due to collapsed arteries and veins. In light of all this, the decision to perform an ECPR requires careful deliberation. In this study, the median CPR time before ECMO onset was 61.5 minutes, which is longer than in other studies [2,4]. However, our survival rate to discharge of 33% was com-

Table 3. Comparison of patients with ECMO weaning success and failure

Variable	ECMO weaning success (n=10)	ECMO weaning failure (n=2)	p-value
Age (mo)	5.6 (range, 0–140.1)	48.1 (range, 20.1–76)	0.637
Weight (kg)	8.7 (range, 2.6–31)	18.5 (range, 11–26)	0.336
Sex			0.999
Male	5 (50)	1 (50)	
Female	5 (50)	1 (50)	
Extracorporeal CPR location			0.091
Heart ICU	8 (80)	0	
Other ICU	2 (20)	2 (100)	
Cannulation site			0.999
Neck	7 (70)	1 (50)	
Central	3 (30)	1 (50)	
ECMO time			0.999
Weekday	8 (80)	2 (100)	
Weeknight	2 (20)	0	
Perioperative period	3 (30)	0	0.999
CPR time (min)	61 (range, 10–86)	84.5 (range, 75–94)	0.109
Cannulation time (min)	31 (range, 18–58)	73.5 (range, 69–78)	0.001
ECMO duration (hr)	125.5 (range, 55–336)	76.5 (range, 2–151)	0.371
Diagnosis			
Single ventricle	3 (30)	0	0.999
Myocarditis	2 (20)	0	0.999

Values are presented as median (range) or number (%).
ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; ICU, intensive care unit.

parable to other studies with survival rates between 33% and 38% [2,4,5]. In this study, the CPR time did not differ between survivors and non-survivors. The performance of effective CPR during the pre-cannulation period is of paramount importance for a good outcome [4].

Five patients who survived more than seven days after support discontinuation later succumbed to death. Patients 1, 5, and 11 had congenital heart disease, and they could not survive due to an irreversible brain injury. Patient 2 had a single functional ventricle. He underwent the ECMO procedure on postoperative day 1 after a shunt operation involving an opened sternum and underwent a successful weaning course. This child could not be weaned from the ventilator, and thus, underwent a second-stage operation (bidirectional cavopulmonary shunt). However, the patient succumbed to sepsis. Patient 7 underwent an ECMO procedure on postnatal day 1 due to obstructive total anomalous pulmonary venous return (TAPVR) and received emergency TAPVR repair. This neonate underwent a successful weaning course of ECMO; however, he re-

quired reoperation for pulmonary vein stenosis and succumbed to sepsis. Surviving more than seven days after ECMO weaning may be interpreted as an indicator of success. However, in this case, neurologic injury during ECPR was the main reason that the favorable outcome did not last longer. Another patient (patient 10) who was successfully weaned but succumbed to death also had severe hypoxic brain injury. Our weaning rate for ECPR was 83.3%, which is better than that of other studies [1,4]; however, many patients who had a successful weaning course died due to brain injury. In the current era, ECMO weaning appears not to be an obstacle itself; however, uncomplicated neurologic injury after ECMO weaning is a major concern. To achieve this goal, we should educate hospital employees on high-quality skills in routine procedures, which is helpful to prevent neurologic injury during ECPR. Regular training with ECPR simulation programs can also lead to the development of a highly functional and well-coordinated team working towards the reduction of the ECMO deployment time [16].

The limitations of the present study include its retrospective nature, and the small number of patients included. In conclusion, ECPR plays a valuable role in children experiencing refractory postoperative cardiac arrest. In our study, the weaning rate was excellent; however, survival was based on other organ dysfunction and the severity of ischemic brain injury. Timely support prior to the emergence of end-organ injury and prevention of neurologic injury may enhance survival.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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