Intensive Care Med (2010) 36:520–527
DOI 10.1007/s00134-009-1739-2

PEDIATRIC ORIGINAL

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Extracorporeal life support for treatment of children with enterovirus 71 infection-related cardiopulmonary failure

Received: 21 May 2009
Accepted: 12 August 2009
Published online: 24 December 2009

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Abstract *Purpose:* Enterovirus 71 (EV71) infection leading to cardiopulmonary failure (CPF) is rare, but usually fatal. In such cases, intensive cardiorespiratory support is essential for survival. In this study, we report our experience in the treatment of EV71-related CPF with extracorporeal life support (ECLS). *Methods:* This was a retrospective study of a total of 13 children, aged 16 ± 10 months, with EV71-related hemodynamically unstable CPF, which was refractory to conventional treatments, who were rescued by transsternal ECLS from 2000 to 2008. The clinical manifestations and outcomes of the 13 children (present cohort) were compared with those of 10 children (past cohort) who had EV71-related CPF without ECLS between 1998 and 2000. *Results:* Among these 13 patients, 10 were successfully weaned off ECLS and survived. The myocardial recovery time was 71 ± 28 (median, 69) h, and the ECLS duration was 93 ± 33 (median, 93) h. Six surviving patients had a good neurological outcome at hospital discharge. All surviving patients had some neurological sequelae but showed improvement at follow-up, including dysphagia in nine, central hypoventilation in seven, limb weakness in six and seizure in three. The present cohort had better neurological outcomes (46 vs. 0%, $P = 0.005$) and a higher survival rate (77 vs. 30%, $P = 0.024$) than the past cohort, respectively. *Conclusions:* Patients with EV71-related CPF supported by ECLS had a higher survival rate and fewer neurological sequelae than those who only received conventional treatments. ECLS is an effective alternative method for treatment of children with refractory EV71-related CPF.

Keywords Cardiopulmonary failure · Enterovirus 71 infection · Extracorporeal life support · Outcome

Introduction

Most of the children with enterovirus 71 (EV71) infections present with hand, foot and mouth disease or herpangina, and only a few children may progress to more serious symptoms, such as central nervous system (CNS) manifestations, pulmonary edema, acute myocardial failure, rapid shock or even death [1–7]. Although many therapeutic strategies for severe EV71 infection have been used, the mortality rates remain between 10 and 25.7% [8–11]. Our previous study in 1998 demonstrated that acute cardiac dyskinesia, low ejection fraction (EF) and regional wall motion abnormalities (RWMA) of the left ventricle (LV) were commonly noted in EV71-related early mortality [4]. Therefore, rapid deterioration and death caused by acute myocardial failure with or without

respiratory failure were proposed as the main cause of EV71-related early mortality [4, 5, 12, 13]. An effective resuscitation modality is therefore required to ensure survival and better outcomes in EV71-infected children presenting with life-threatening cardiopulmonary complications. With the application of extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices, outcomes for critically ill infants and children have continuously improved over the past decade [14–16]. However, clinical experience in the use of these modalities remains limited for resuscitation of children with EV71-related cardiopulmonary failure (CPF) [17, 18]. In 2000, we firstly utilized a centrifugal left ventricular support to successfully rescue a toddler with EV71-related fulminant myocardial failure [17]. Thereafter, extracorporeal life support (ECLS) offered an alternative method of intensive cardiorespiratory resuscitation for children with late-stage severe EV71 infections that were unresponsive to conventional treatment modalities in our institute. In this study, we report our experience in the treatment of severe EV71 infections with ECLS from 2000 to 2008, which was presented at the Fifth World Congresses of Pediatric Cardiology and Cardiac Surgery in 2009 and published as a poster abstract.

Patients and methods

Patient population

From 2000 to 2008, a total of 170 children with severe EV71 infections were clinically diagnosed to have laboratory-confirmed EV71 infection. The methods used to identify EV71 were the same as those described by Fu et al. [5]. Viral identification was simultaneously confirmed by the Taiwan Centers for Disease Control. Children with severe EV71 infection presented either with preceding hand, foot and mouth disease or herpangina plus CNS involvement with or without subsequent CPF or shock. According to a previous clinical report [8], the clinical features of EV71 infection can be divided into four stages: hand, foot and mouth disease/herpangina (stage 1), CNS involvement (stage 2), cardiopulmonary failure (stage 3) and convalescence (stage 4). Stage 3 is subdivided into stage 3a (coexisting with hypertension) and stage 3b (coexisting with hypotension). Among the 170 children, a total of 13 with severe EV71 infection presented with subsequent CPF (stage 3) requiring intensive cardiorespiratory support (Table 1). They were all hemodynamically unstable and refractory to conventional medical treatments, which included fluid therapy,

Table 1 Comparison between past and present, stage 3a and stage 3b cohort data: demographic, initial laboratory features and outcomes of patients with critical EV71-related cardiopulmonary failure

	Past cohort (1998–2000) ($n = 10$)	Present cohort (2000–2008) ($n = 13$)	*P* value	Present cohort EV71-stage 3a ($n = 8$)	Present cohort EV71-stage 3b ($n = 5$)	*P* value
Management	Conventional	ECLS		ECMO (5)/ECLVS (3)	ECMO (5)	
Age (months)	18 ± 14 (13)	16 ± 10 (16)	0.901	16 ± 12 (13)	16 ± 7 (18)	0.883
Gender	5M/5F	9M/4F	0.349	5M/3F	4M/1F	0.506
BW (kg)	10 ± 3 (10)	10 ± 3 (10)	0.901	10 ± 3 (10)	11 ± 3 (11)	0.604
Onset to admission (day)	4 ± 1 (4)	3 ± 1 (3)	0.139	3 ± 1 (3)	3 ± 1 (3)	0.503
MaxHR (bpm)	204 ± 37 (209)	213 ± 22 (205)	0.756	202 ± 15 (200)	230 ± 20 (220)	0.012*
MaxSBP (mmHg)	117 ± 15 (118)	106 ± 40 (126)	0.509	132 ± 11 (31)	56 ± 22 (59)	0.006*
CTR in CxR	0.50 ± 0.06 (0.51)	0.51 ± 0.04 (0.51)	0.876	0.52 ± 0.03 (0.52)	0.49 ± 0.05 (0.49)	0.295
LVEDD, *Z* score	0.9 ± 1.9 (1.0)	1.2 ± 2.4 (0.2)	0.804	0.91 ± 2.1 (0.1)	1.6 ± 3.0 (2.6)	0.660
Initial EF%	38 ± 14 (36)	33 ± 9 (34)	0.576	33 ± 7 (33)	32 ± 11 (39)	0.941
CK (IU/l)	344 ± 445 (183)	333 ± 162 (369)	0.222	316 ± 168 (357)	368 ± 167 (416)	0.552
CK-MB (IU/l)	13.7 ± 11.9 (11)	19.8 ± 10 (20)	0.364	19.5 ± 7.4 (20.9)	20.3 ± 21.9 (15.1)	0.831
Glucose (mg/dl)	251 ± 137 (232)	323 ± 308 (181)	0.776	236 ± 203 (125)	444 ± 408 (237)	0.465
Pulmonary edema	9 (90%)	11 (85%)	0.709	6 (75%)	5 (100%)	0.224
Good neurological outcome	0 (0%)	6 (46%)	0.005*	6 (75%)	0 (0%)	0.002*
Survival rate (>7 days)	30% 7 Early deaths 3 Late deaths	77% 3 Early deaths 1 Late death	0.024*	100% All survived	40% 3 Early deaths 1 Late death	0.012*

Data are presented as mean ± standard deviation (median) or case numbers (%). Good neurological outcome is defined survival to discharge with PCPC of 1, 2 or 3 at hospital discharge or no change from pre-ECLS PCPC. *P* value is assessed by comparisons of data between past and present, stage 3a and 3b cohorts

BW body weight, *CK* creatine kinase, *CK-MB* muscle-brain fraction of creatine kinase, *CTR* cardiothoracic ratio, *CXR* chest X-ray, *ECMO* extracorporeal membrane oxygenation, *ECLVS* extracorporeal left ventricular support, *EF* ejection fraction of the left ventricle, *EV* enterovirus, *MaxHR* maximum heart rate, *LVEDD* left ventricular end-diastolic dimension, *MaxSBP* maximum systolic blood pressure

* $P < 0.05$

intravenous inotropic agents and mechanical ventilation support. Those patients were then rescued by transsternal ECLS when they experienced rapid deterioration of cardiac function with an LVEF of less than 40% and preexisting systemic hypertension with subsequent systolic blood pressure depression of more than 20% within 1 h (stage 3a) or decompensated cardiopulmonary function and shock (stage 3b). Ten children (past cohort) with EV71-related CPF who received conventional medical treatments without ECLS therapy between 1998 and 2000 were compared to the present cohort (Table 1).

ECLS protocol

All patients received chest cannulation in the operating room (patient nos. 1, 2, 3, 9) or intensive care unit setting. In this study, the ECLS circuit included ECMO with LV vent and extracorporeal left ventricular support (ECLVS). In patients who received ECMO with LV decompression, the cannulation was performed by placing the tip of the venous cannula in the right atrium directly through the open chest. A LV cannula was placed through the left atrium to separately decompress the left-sided heart. The arterial cannula was placed into the ascending aorta directly through the open chest. In patients who received ECLVS, a LV cannula was placed to decompress the left side of the heart separately. The arterial cannula was placed into the ascending aorta directly through the open chest. The Capiox emergent bypass system (Terumo Inc., Tokyo, Japan) was used, and the ECLS circuit consisted of a centrifugal pump, heat exchanger, and transsternal cannulas with or without a hollow-fiber microporous polypropylene membrane oxygenator. Anticoagulation was maintained with intravenous heparin to keep the activated clotting time at 180 to 220 s. Platelet count and the hemoglobin level were maintained above 100,000/μl and 10 mg/dl. The primary goal of ECLS therapy usually is to restore and maintain optimal tissue perfusion while cardiac recovery takes place and maintain a urine output of greater than 1 ml/kg/h and a brisk capillary refill. The mechanical ventilator settings were reduced to "rest settings" if the patient was totally bypassed without any major cardiac contribution to the total systemic flow. The patient's temperature was maintained as close to normothermia as possible. Transthoracic echocardiography was performed within 30 min of admission to the PICU and daily follow-up to detect the recovery of myocardial function. The weaning process was begun if cardiac systolic function was restored to at least 55% of LVEF with adequate end-organ perfusion.

Outcome measures

The primary outcome measurement was survival-to-hospital discharge, and the secondary outcome measurement was survival-to-discharge with good neurological outcome. Neurological outcomes were determined using the pediatric cerebral performance category (PCPC) scale [19]. The PCPC scoring is as follows: 1, normal age-appropriate neurodevelopmental functioning; 2, mild cerebral disability; 3, moderate cerebral disability; 4, severe disability; 5, coma/vegetative state; 6, brain death. Categorizations at the time of hospital discharge and 6-month follow-up assessment after discharge were determined. Good neurological outcome is defined as survival to discharge with a PCPC score of 1, 2 or 3 at hospital discharge in comparison to the most of the EV-71 stage 3 children receiving conventional treatments with bad neurological outcomes [2, 20, 21].

Data collection and statistical analysis

Data are presented as median, mean ± standard deviation, case numbers or percentages. Statistical analysis was performed with SPSS, version 15.0 for Windows (SPSS, Chicago, IL). Comparisons of data of clinical manifestations, laboratory features and outcomes between past and present cohorts and between EV71 stage 3a and 3b were assessed with Mann-Whitney *U* test, Pearson's chi-square test or chi-square test for trends. The survival rate of patients with EV71-related CPF was estimated by the Kaplan–Meier method. The difference between stage 3a and stage 3b was evaluated by using the log-rank test. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

The demographic data, clinical manifestations and outcomes of patients are presented in Tables 1 and 2. Acute CPF occurred in patients 2–4 days after enterovirus infection symptoms. All 13 patients had tachypnea, and tachycardia with a maximum heart rate ranged from 185 to 260 bpm. Eight (62%) patients, who presented as EV71 stage 3a on arrival to the PICU, had preexisting systemic hypertension with maximum systolic blood pressure ranging from 119 to 156 mmHg, and the other 5 (38%) patients presented as EV71 stage 3b with hypotension. Eleven (85%) patients had pulmonary edema. None of them had cardiomegaly on chest radiograms, but all had typical RWMA and poor LV systolic function by echocardiography. The cardiothoracic ratio calculated from the chest radiography ranged from 0.43 to 0.55. *Z* score of the LV end-diastolic diameter ranged from −2.1 to 4.6 by echocardiography. Initial abnormal LVEF ranged from 17 to 46% and pre-ECLS follow-up LVEF of 10 to 40%.

Four (31%) patients had cardiopulmonary resuscitation prior to receiving ECLS and were rescued by ECMO after return of spontaneous circulation.

ECLS treatment

Among the 13 patients rescued by ECLS, 3 were placed on ECLVS, and 10 were placed on ECMO. Ten (77%) patients were weaned off ECLS and survived EV71-related CPF, but one patient died at 157 days after wean-off from ECLS (late death) because of encephalopathy. Three patients died of cardiopulmonary failure with subsequent multiple organ failure, including two patients who died before the recovery of myocardial function and one who died despite restoration of myocardial function while on the device 38, 72 and 135 h after initiation, respectively (early death). The recovery time of myocardial function (LVEF >55%) ranged from 21 to 111 h (mean 71 ± 28, median 69 h). The weaning process ranged from 6 to 48 h (mean 27 ± 12, median 24 h). Total duration of ECLS implantation ranged from 38 to 145 h (mean 93 ± 33, median of 93 h) with a maximum bypass flow rate of 1.5–3 l/min/m^2. Total duration of PICU stay ranged from 3 to 162 days (mean 47 ± 44, median 26 days), and total hospital stay ranged from 3 to 394 days (mean 92 ± 114, median 29 days). Table 3 summarizes the complications of ECLS treatment. Metabolic and bleeding complications occurred in all patients, including 11 (85%) patients who required wound re-exploration. Five (38%) patients had nosocomial infections, such as pneumonia, bacteremia and urinary tract infection. Three patients had acute renal failure after receiving ECLS 48 h, and two patients needed subsequent hemodialysis. Abnormal blood sugar levels and acute renal failure occurred more commonly in patients with stage 3b than stage 3a after ECLS. The results of neurological outcomes are shown in Table 2. Among ten surviving patients, six had a good neurological outcome at hospital discharge, and five patients had improved at the 6-month follow-up assessment according to the PCPC score.

Comparison of present and past cohorts

The data of the present and past cohorts are compared in Table 1. Seven (70%) and three (23%) patients had early death because of multiple organ failure, and three (30%) patients and one (8%) patient had late death because of encephalopathy in both groups, respectively. Patients in the present cohort had better neurological outcomes (good neurological outcomes of 46 vs. 0%, $P = 0.005$) and higher survival rates (survival rate of 77 vs. 30%, $P = 0.024$) than those in the past cohort, respectively.

Comparison of stage 3a and 3b cohorts

In this study, stage 3a patients had statistically lower maximum heart rate, higher systolic blood pressure, lower incidence of elevated blood creatinine level 48 h after ECLS, higher survival rate and better neurological outcomes than stage 3b patients (Table 2). Cumulative survival curves for EV71 stage 3, 3a and 3b patients are shown in Fig. 1. Three (60%) stage 3b patients had early death. The other two (40%) stage 3b patients had severe neurological sequelae, such as deep coma, dysphagia requiring tube feeding, central hypoventilation requiring tracheostomy and long-term mechanical ventilation support, and late death (one patient). In contrast with the stage 3b patients, all of the stage 3a patients survived and had better PCPC scores at hospital discharge and 6-month follow-up after discharge. Their neurological sequelae subsided gradually, and the duration of follow-up ranged from 6 months to 8 years (mean 880 ± 676 days, median 1,822 days).

Discussion

Clinical presentation of EV71-related CPF

Children with EV71 infections typically have hand, foot and mouth disease or herpangina, but only a few patients, less than 0.1%, progress to severe EV71 infection. Subsequent acute CPF occurred in 11–19% of severe EV71-infected children when the CNS was involved, resulting in a mortality rate of 30–77% and severe neurological sequelae [1–12]. Clinical manifestations, such as tachycardia, tachypnea, diaphoresis, arrhythmia, pulmonary edema and myocardial dysfunction, of EV71-related acute CPF in children mimic those of acute viral myocarditis associated with pulmonary edema. However, distinctive neurological symptoms, preexisting systemic hypertension, no cardiomegaly on chest roentgenography, LV hypokinesia with RWMA, rapid shock and quick death are characteristic of EV71-related acute CPF [4–6, 12, 17, 18]. Fu et al. [5] proposed that the most likely cause of acute cardiopulmonary complications after EV71 infection is excessive catecholamine release. The clinical findings of patterns of RWMA, called "panic or shivering heart," may correlate with the distribution of myocardial sympathetic nerve terminals [22, 23].

ECLS therapy and complications

The distinctive feature of this study is certainly the use of extracorporeal mechanical assistance to support cardiopulmonary function in children with EV71-related CPF. Severe acute myocardial dysfunction in severe EV71

Table 2 Characteristics and outcomes of patients with EV71-related cardiopulmonary failure rescued by ECLS

No	EV stage	Pre-ECLS Mx				Mode	ECLS						Survival	Outcomes			
		EF%	CPR	IVIG	Milrinone		48 h Cr	48 h ALT	EF >55% (h)	Total ECLS (h)	Wean off	ICU stay (day)		PCPC at HD	PCPC 6 m	MRI/CT	Neurologic sequelae
1	3a	27	−	+	+	ECLVS	1.0	65	21	57	+	50	+	2	1	BEM, Inf	D/H/S/W
2	3a	18	−	+	−	ECLVS	0.8	156	49	73	+	73	+	4	4	BE, ICH	D/H/S/W
3	3a	37	+	+	+	ECMO	0.8	68	70	94	+	26	+	2	1	BEM	D
4	3a	34	−	+	+	ECLVS	0.8	20	69	93	+	39	+	4	4	BEM	D/H/W
5	3a	31	−	−	+	ECMO	0.6	19	84	90	+	83	+	3	2	BEM	D/H/W
6	3a	31	−	+	+	ECMO	0.7	30	36	60	+	16	+	1	1	BE	D
7	3a	26	−	−	−	ECMO	0.4	13	102	126	+	55	+	2	1	BEM	D/H
8	3a	25	−	−	+	ECMO	0.3	34	97	145	+	17	+	2	2	BE	S/W
9	3b	28	−	−	+	ECMO	0.6	8	111	135	−	8	E	NA	NA	NA	NA
10	3b	22	+	+	+	ECMO	2.2	NA	NA	72	−	4	E	NA	NA	NA	NA
11	3b	40	−	+	+	ECMO	2.3	1161	NA	38	−	3	E	NA	NA	NA	NA
12	3b	28	+	−	+	ECMO	2.7	40	76	102	+	71	+	5	5	BE, Inf	D/H/S/W
13	3b	10	+	+	+	ECMO	0.9	27	66	124	+	162	L	5	NA	BEM, ICH	D/H/W
P value		0.660	0.071	0.928	0.224		0.047*	1.0									

P value is assessed by comparisons of cohort data between EV71 stage 3a and 3b

ALT alanine aminotransferase, *BE* brainstem encephalitis, *BEM* brainstem encephalomyelitis, *CPR* cardiopulmonary resuscitation, *Cr* creatinine, *D* dysphagia, *E* early mortality, *ECLS* extracorporeal life support system, *ECLVS* extracorporeal left ventricular support, *ECMO* extracorporeal membrane oxygenation, *EF* ejection fraction of the left ventricle, *EV71* enterovirus 71, *H* central hypoventilation, *HD* hospital discharge, *ICH* intracranial hemorrhage, *ICU* intensive care unit, *Inf* brain infarction, *IVIG* intravenous immunoglobulin, *L* late mortality, *MRI/CT* magnetic resonance imaging and/or computed tomography, *NA* not available, *PCPC* pediatric cerebral performance category, *PE* pulmonary edema, *6m* 6-month follow-up after hospital discharge, *S* seizure, *W* limb weakness

* $P < 0.05$

Table 3 Complications of ECLS treatment

Variable	Total ($n = 13$)
Bleeding	13 (100%)
Cardiac tamponade	4 (31%)
Required wound re-exploration	11 (85%)
Hematologic: anemia/thrombocytopenia	11 (85%)
Culture-proven infection	5 (38%)
Acute renal failure after ECLS 48 h	3 (23%)
Required hemodialysis	2 (15%)
Hepatic failure after ECLS 48 h	1 (8%)
Arrhythmia	2 (15%)
Neurological[a]	5 (38%)
ICH	2 (15%)
Brain infarction	2 (15%)
Seizure[b]	3 (23%)
Metabolic	13 (100%)
Alkalosis	8 (62%)
Acidosis	2 (15%)
Hypolgycemia	4 (31%)
Hyperglycemia	7 (54%)
Hypocalcemia	13 (100%)
Hypoalbuminemia	7 (54%)
Mechanical	3 (23%)
Blood clot or air circuit	3 (23%)
Cannula kinking	1 (8%)

P value is assessed by comparisons of cohort data between EV71 stage 3a and 3b

ICH intracranial hemorrhage, *ECLS* extracorporeal life support system

* $P < 0.05$

[a] Three patients in stage 3b could not be evaluated for neurological complications due to early death

[b] EV71-related or ECLS-related

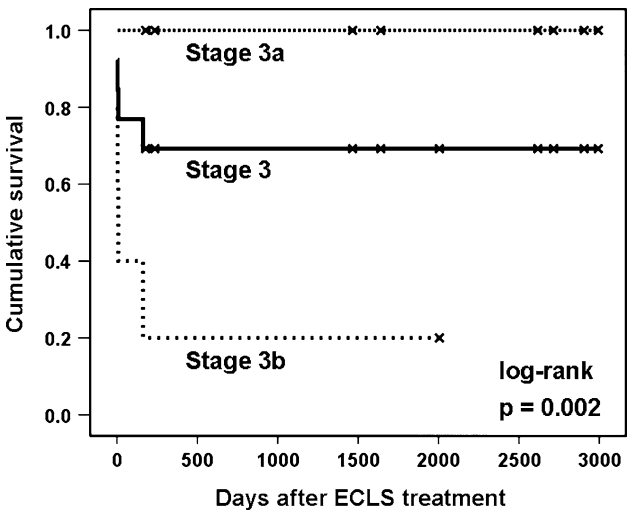

Fig. 1 Kaplan-Meier plot of the survival curves for the patients with stage 3, stage 3a and 3b enterovirus 71 infections. A significant difference between stage 3a and 3b was noted. *ECLS* extracorporeal life support

patients is taken as an ominous sign of rapid deterioration and poor prognosis. Without mechanical support, 71–83% of patients die within 12–24 h after the onset of CPF, and those who survive may have severe neurological sequelae [2–6]. However, acute CPF usually is transient and quickly reversible if an optimal treatment that can maintain hemodynamic stability and restore heart function to improve end-organ perfusion is initiated. In this study, the median recovery time of myocardial function and the median duration of mechanical circulatory support were 69 and 93 h, respectively. These durations were shorter than those for children with acute myocarditis rescued by mechanical support, with the mean duration of mechanical circulatory support ranging from 115 to 140 h [24, 25]. Some authors proposed that a very high dose of inotropic agents or such agents combined with milrinone may improve survival for some patients with EV71-related CPF [7, 10]; however, individual clinical manifestations and outcomes were not described clearly in their reports. According to the catecholamine-mediated hypothesis for EV71-related CPF, we were concerned that catecholamine toxicity would be reinforced and harmful if higher doses of inotropic agents were used. In this study, we usually used moderate dosages of inotropes before ECLS. Administration of IVIG was suggested by the Taiwan Centers for Disease Control for patients with severe EV71 infection; however, previous studies found generally lower neutralization titers in many different commercial IVIG preparations containing antibodies against different enteroviruses, and outcomes cannot be predicted from the incidence of any particular serotype circulating in the community [26, 27]. Steroids are also not suggested for use in children with EV71 infection because they may trigger acute heart failure presumably by augmenting the sensitivity of myocardial cells to catecholamine [28]. Therefore, ECLS can be considered as the treatment of choice for EV71-related acute CPF pending recovery of myocardial function and pulmonary edema if patients are unresponsive to conventional medical treatments.

The ECLS modalities used in this study included ECMO and ECLVS. ECMO was used in children with severe EV71 infection to provide full cardiopulmonary support, whereas ECLVS in these patients was used to support a failing heart. In the early treatment period, patients with stage 3a infection (case nos. 1, 2 and 4) were supported by ECLVS because our priority was cardiac support to relieve pulmonary edema. We did not need to consider the limited life span of the oxygenator because we did not know how long the myocardial recovery time would be. Patients with stage 3b infection or those who had received cardiopulmonary resuscitation prior to ECLS (case nos. 3, 10, 12 and 13) were rescued by ECMO because their infection was more severe and they needed total cardiorespiratory support. As our experience in critical care of EV71-infected patients grew, we found that mechanical support was only needed for a short period of time; hence, the limited life span of the oxygenator was not an important factor. Some patients had acute

myocardial dysfunction associated with severe respiratory distress, especially patients with stage 3b infection, and some patients had progressive deterioration of the pulmonary condition during ECLVS. The reason for the progressive deterioration of the pulmonary condition during ECLVS could be due to the inflammatory response to the extracorporeal circuit, or a reaction to massive transfusion because of bleeding, or an ongoing neurogenic pulmonary edema. We preferred to treat these patients with total cardiorespiratory support. In addition, left-sided cardiac decompression was usually needed because of severe prolonged pulmonary edema, left-heart overload and thrombus formation in LV caused by a dilated, poorly contracting LV and raised afterload if ECMO was used without left heart decompression. Therefore, in the late treatment period, we preferred transsternal ECMO with LV vent for both effective total cardiopulmonary support and left-sided cardiac decompression in severe EV71 patients with CPF, especially stage 3b patients, instead of ECLVS and peripheral ECMO without left heart decompression despite the potential for complications such as mediastinal bleeding and infection.

In this study, the most common complications of ECLS treatment were mediastinal bleeding and hypocalcemia. Because of transsternal cannulation, wound re-exploration was usually required to check bleeding, and massive blood transfusion was usually necessary, which could be the reason for hypocalcemia. Cerebral complications are among the most serious complications of ECLS treatment, because they determine survival rates, neurological outcome and can have great impact on the quality of life. However, some complications may already have occurred or may not have been detected before the start of ECLS. Therefore, it is sometimes difficult to differentiate between EV71-related and ECLS-related complications.

Survival and neurological outcome

According to the epidemiologic reports of the Taiwan Centers for Disease Control from 1998 to 2008, the overall case mortality rate was 21.2% (128/603) from 1998 to 2000 and 12.3% (131/1,061) from 2001 to 2008. In our study, the mortality rate for severe EV71 infection was 24.4% (10/41) from 1998 to 2000 for patients receiving conventional medical treatments, and the rate decreased to 2.3% (4/170) after treatment with ECLS. Although patients with severe EV71 infection could be rescued by ECLS, various degrees of neurological sequelae occurred. They could be caused by EV71-related brain stem encephalomyelitis, shock and CPR-related hypoxia-ischemia encephalopathy or ECLS-related CNS complications. In general, neurological sequelae occurred more frequently in stage 3b patients associated with more severe disease states or pre-ECLS cardiopulmonary resuscitation than stage 3a patients, and that increased the risk of cerebral damage and acute renal failure after ECLS treatment. These results suggest that ECLS is beneficial for patients with EV71-related CPF. Early intervention can minimize the rate of shock, reduce CPR-related and ECLS-related complications, and lead to a good neurological and survival outcome.

Conclusions

In this study, we demonstrated that children with EV71-related CPF who received ECLS had a higher survival rate and fewer neurological sequelae than those who only received conventional medical treatments. Our experience suggests that ECLS is an effective alternative method for treating children with early EV71-related CPF, but it would be controversial in patients with a history of shock or cardiopulmonary resuscitation prior to ECLS.

Acknowledgments We would like to thank Chi-Ren Tsai, Li-Cheng Wang and the Taiwan Centers for Disease Control for their identification of enterovirus. We are also grateful to all our colleagues in the Department of Pediatrics and Department of Cardiovascular Surgery, Taichung Veterans General Hospital, for their help. The authors declare that no financial support was received for this study

Conflict of interest statement The manuscript does not have any potential conflict of interest, real or perceived, and did not have a study sponsor.

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