Prognosis in the Patients with Prolonged Extracorporeal Membrane Oxygenation

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Background: Prolonged usage of extracorporeal membrane oxygenation (ECMO) may induce multi-organ failure. This study is aimed to evaluate prognostic factors in the patients with ECMO. Also, the prognosis of ECMO with Kidney Injury Network Scoring system is studied. **Materials and Methods:** From May 2005 to July 2011, 172 cases of ECMO were performed. The cases of perioperative use of ECMO were excluded. Renal failure patient and younger than 15 years old one were also excluded. As a result, 26 cases were enrolled in this study. Male patients were 15 (57.7%), and mean age was 56.57±17.03 years old. Demographic data, ECMO parameters, weaning from ECMO, and application of continuous renal replacement therapy are collected and Acute Kidney Injury Network (AKIN) scores were evaluated just before ECMO and day 1, day 2 during application of ECMO. **Results:** Venoarterial ECMO was applied in 22 cases (84.6%). The reasons for applications of ECMO were cardiac origin in 21 (80.8%), acute respiratory distress syndrome in 4, and septic shock in 1 case. Successful weaning from ECMO was achieved in 15 cases (57.7%), and survival discharge rate was 9 cases (34.6%). Mean duration of application of ECMO was 111.39±54.06 hours. In univariate analysis, myocarditis was independent risk factors on weaning failure. Using the receiver operating characteristic curve, level of hemoglobin on 24 hours after ECMO, and base excess on 48 hours after ECMO were showed more than 0.7. AKIN score was not matched the prognosis of the patients with ECMO. **Conclusion:** In our study, the prognosis of the patients with myocarditis was poor. Hemoglobin level at first 24 hours, and degree of acidosis at 48 hours were useful methods in relating with prognosis of ECMO. AKIN scoring system was not related with the prognosis of the patients. Further study for prognosis and organ injury during application ECMO may be needed.

Key words: 1. Prognosis
2. Extracorporeal membrane oxygenation

INTRODUCTION

According to the data from Extracorporeal Life Support Organization registry, successful weaning rate from extracorporeal membrane oxygenation (ECMO) is 57%, and overall survival discharge rate is 46% in adult patients (Fig. 1) [1]. Data from Health Insurance Review and Assessment Service of Korea shows total cases of ECMO have been increasing since 2006 (Fig. 2). Prolonged operation of ECMO may produce many complications. Among them, organ damages may play an important role for the prognosis of the patients with ECMO. New devices, reducing the possibility of

complications, have been developed and used. But, there is no perfect device that would not damage organs. Recently, some authors reported that scoring system for renal injury is good predictor for ECMO patients [2]. We reviewed our cases of ECMO to find the prognostic factor. To find the relationship between organ damages and prognosis of the patients with ECMO, the known scoring system was applied, which was proposed by Acute Kidney Injury Network group (Table 1) [3].

MATERIALS AND METHODS

From May 2005 to July 2011, 172 cases of ECMO were performed in Seoul National University Bundang Hospital. Total cases of ECMO that had operated more than 48 hours are 76. Because of the possibility of cardiopulmonary bypass

effect during open heart surgery, the cases of perioperative application of ECMO were excluded. Known renal failure patients with hemo-dialysis were also excluded. Severity of disease classification system (SAPS) II was designed to estimate the severity of disease for patients [4], who admitted intensive care unit aged 15 or more, cases of younger than this were also excluded. Finally, twenty-six patients were enrolled in this study (Fig. 3). Male patients were 15 (57.7%), and female 11 (42.3%). Mean age was 56.57 (standard deviation, ±17.03) (range, 20 to 84) years old. Patients were divided into two groups, ECMO weaning success group and failure group. Body weight, smoking history, presence of diabetes, hypertension, and history of cerebrovascular accident were checked. Hemoglobin and serum creatinine levels at the time of admission, 24 and 48 hours after initiation of ECMO were checked. Platelet counts, level of aspartate aminotransferase (AST), total bilirubin, glucose, and albumin 24 and 48 hours after initiation of ECMO were also checked. Base excess, reflecting degree of metabolic acidosis, mean arterial pressure,
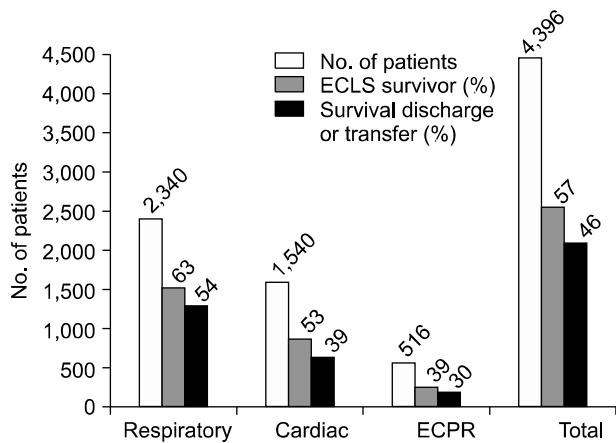

Fig. 1. Overall outcomes in adult extracorporeal membrane oxygenation patients. Data from the Extracorporeal Life Support Organization registry (till July 2011). ECLS, extracorporeal life supports; ECPR, extracorporeal cardiopulmonary resuscitation (Modified from Dalton HJ. Respir Care 2011;56:1445-53, with permission from Daedalus Enterprises Inc.) [1].
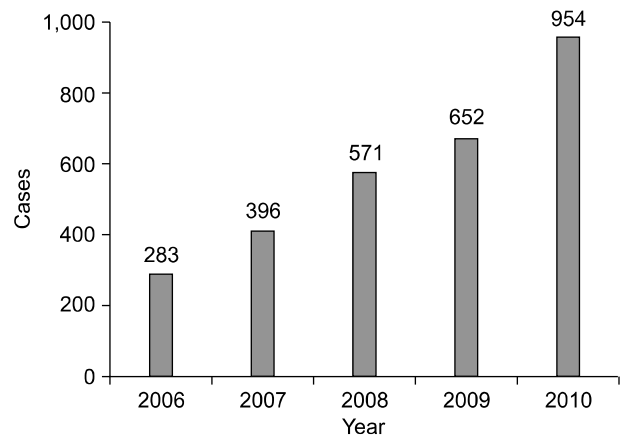
Fig. 2. Yearly cases of extracorporeal membrane oxygenation in Korea. A data from Health Insurance Review and Assessment Service of Korea.

Table 1. Acute Kidney Injury Network scoring system

Stage	Creatinine criteria	Urine output criteria
Stage 1	Increase in serum creatinine ≥0.3 mg/dL or increase ≥1.5 times from baseline	≤0.5 mL/kg/hr for more than 6 hr
Stage 2	Increase in serum creatinine ≥2-fold from baseline	≤0.5 mL/kg/hr for more than 12 hr
Stage 3	Increase in serum creatinine ≥3-fold from baseline or serum creatinine ≥4.0 mg/dL and initation of renal replacement therapy	≤0.3 mL/kg/hr for more than 24 hr

Fig. 3. Inclusion and exclusion criteria and distribution by sex. ECMO, extracorporeal membrane oxygenation; CRF, chronic renal failure; HD, hemodialysis; SAPS, severity of disease classification system.

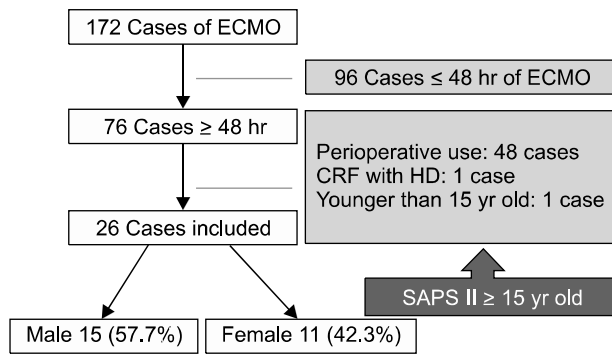flows of ECMO at the time of starting, 24 and 48 hours of ECMO were investigated. Regarding to ECMO, changes of body weight after 48 hours, the amounts of transfusion, types (venoarterial or venovenous), insertion place, and relation with cardiopulmonary resuscitation, operating duration, and application of continuous renal replacement therapy were evaluated. Vasoactive agents, sequential organ failure assessment (SOFA), and SAPS II scores were calculated. Acute Kidney Injury Network (AKIN) scores were calculated and applied for each stage of initiation; $AKIN_{0-hours}$, 24; $AKIN_{24-hours}$, and 48 hours of ECMO; $AKIN_{48-hours}$ (Table 1).

Descriptive statistics for continuous variables are expressed as mean±standard deviation. And categorical variables are expressed as frequency and percentage. All variables were tested for normal distributions using the Kolmogorov-Smirnov test. The Student t-test was applied to compare means of continuous variables. Categorical data were tested using the χ^2 test or Fisher's extract test. Statistical significance were considered if p-values were less than 0.05 ($p < 0.05$). Univariate analysis and linear regression were performed. This study is approved by the institutional review board of Seoul National University Bundang Hospital, Seongnam, Korea.

RESULTS

Venoarterial ECMO was applied in 22 (84.6%) and venovenous in 4 cases. The reasons for applications of ECMO were cardiac arrest in 12, cardiogenic shock in 9, respiratory

Table 2. Comparison between successful weaning of extracorporeal membrane oxygenation and weaning failure groups

	Weaning success group	Weaning failure group	p-value
Sex (male:female)	10:5	5:6	0.426
Age (yr)	58.0±17.70	54.6±16.72	0.629
Body weight (kg)	62.9±11.96	60.2±11.81	0.574
Cardiac arrest	6	6	0.692
Cardiogenic shock	2	7	0.217
Respiratory failure	2	2	0.574
Septic shock	1	0	0.423
Myocarditis	0	4	0.022
Hypertension	4	9	0.428
Diabetes mellitus	3	3	1.0
Smoker	3	5	1.0

Table 3. The results of Acute Kidney Injury Network (AKIN) scoring system in both groups

	Weaning success group	Weaning failure group	p-value
$AKIN_{0-hours}$ 0, 1/2, 3	13/2	9/2	0.735
$AKIN_{24-hours}$ 0, 1/2, 3	12/3	8/3	0.664
$AKIN_{48-hours}$ 0, 1/2, 3	11/4	5/6	0.149

failure in 4, and septic shock in 1. Ventricular tachycardia was classified as cardiac arrest. Patients with myocarditis were 4, who presented with cardiogenic shock in 2 and cardiac arrest in 2. During this period, left ventricular vent were not done for myocarditis. Successful weaning from ECMO was achieved in 15 cases (57.7%), and survival discharge rate was 34.6% (9 cases) in this group. Overall mortality rate was 65.4%. In the weaning success group, there were 10 cases of male patients and 5 of female. In the group of weaning failure, male was 5 and female was 6 cases. There were no statistically difference in sex, age, body weight, hypertension, diabetes, smoking, and preceding diseases for initiation of ECMO, except myocarditis (Table 2). Mean duration of application of ECMO was 111.39±54.06 hours (range, 48.22 to 267.97 hours). In univariate analysis, myocarditis (p=0.022) was the only independent risk factors on weaning failure. Hemoglobin level at 24 hours after initation of ECMO showed equivocal significance of p-value 0.05. Changes in platelet counts, level of AST, total bilirubin, glucose, and al-

Table 4. AUROC

	AUROC±SE	p-value	95% CI		AUROC±SE	p-value	95% CI
AdmHb	0.691±0.112	0.102	0.472−0.910	ECMOFlow48	0.539±0.116	0.736	0.311−0.768
ECMO24Hb	0.827±0.088	0.005	0.655−0.999	BwtECMO48	0.618±0.117	0.312	0.388−0.848
ECMO24Plt	0.515±0.117	0.897	0.285−0.745	DurationHr	0.485±0.118	0.897	0.254−0.715
ECMO24Glu	0.421±0.114	0.500	0.198−0.644	IS0	0.642±0.115	0.223	0.416−0.869
ECMO24Alb	0.524±0.117	0.836	0.295−0.754	IS24	0.373±0.114	0.276	0.150−0.595
ECMO24TB	0.436±0.117	0.586	0.207−0.666	IS48	0.294±0.111	0.078	0.076−0.512
ECMO24AST	0.612±0.122	0.337	0.373−0.851	VIS0	0.509±0.123	0.938	0.268−0.750
ECMO48Glu	0.400±0.114	0.392	0.176−0.624	VIS24	0.391±0.117	0.350	0.162−0.620
ECMO48Alb	0.376±0.113	0.287	0.153−0.598	VIS48	0.358±0.116	0.223	0.130−0.585
ECMO48TB	0.376±0.124	0.287	0.133−0.618	ECMO0Cr	0.530±0.116	0.795	0.303−0.757
ECMO48AST	0.273±0.117	0.052	0.043−0.503	ECMO24Cr	0.439±0.124	0.604	0.197−0.682
BE0	0.406±0.123	0.421	0.166−0.646	ECMO48Cr	0.318±0.116	0.119	0.091−0.545
BE24	0.576±0.121	0.517	0.340−0.812	AKIN0	0.485±0.117	0.897	0.256−0.714
BE48	0.761±0.098	0.026	0.569−0.952	AKIN24	0.506±0.121	0.959	0.268−0.744
MAP0	0.588±0.113	0.452	0.366−0.810	AKIN48	0.361±0.114	0.233	0.136−0.585
MAP24	0.521±0.119	0.856	0.288−0.755	SAPS2	0.470±0.125	0.795	0.224−0.716
MAP48	0.521±0.134	0.856	0.259−0.783	SOFA0	0.579±0.119	0.500	0.346−0.811
ECMOFlow0	0.491±0.118	0.938	0.260−0.721	SOFA24	0.364±0.114	0.243	0.141−0.587
ECMOFlow24	0.448±0.115	0.659	0.222−0.675	SOFA48	0.300±0.104	0.087	0.096−0.504

Numerals indicate hours after initiation of ECMO (for example ECMO24Hb is hemoglobin level 24 hours after initiation of ECMO). AUROC, area under receiver of characteristics; SE, standard error; CI, confidence interval; Adm, admission; Hb, hemoglobin; ECMO, extracorporeal membrane oxygenation; Bwt, body weight; Plt, platelet counts; DurationHr, operating time of ECMO by hour; Glu, glucosel; IS, Wernovsky inotropic score; Alb, albumin; TB, total bilirubin; AST, aspartate aminotransferase; VIS, vaso-active inotropic score; Cr, creatinine; BE, base; AKIN, Acute Kidney Injury Network score; MAP, mean arterial pressure; SAPS2, severity of disease classification system II; SOFA, sequential organ failure assessment.

Table 5. Patients died after successful weaning of ECMO

Number	Sex/age	Indication of ECMO	Duration of ECMO	Duration from weaning to death	Cause of death
1	Male/72	Cardiogenic shock (myocarditis)	5 day	14 day	ARF, ARDS, sepsis
2	Male/64	Recurrent cardiac arrest (R/O PTE)	4 day	2 hr 35 min	R/O recurrence of PTE
3	Male/64	Recurrent VT (AMI)	7 day	2 day	Sustained ventricular fibrillation
4	Male/52	Cardiac arrest (STEMI)	6 day	4 hr	Ventricular arrhythmia
5	Female/49	Respiratory failure (interstitial pneumonia) Considering lung TPL	4 day	4 day	ARF, DIC
6	Male/54	Cardiogenic shock (STEMI)	6 day	20 day	Septic shock

ECMO, extracorporeal membrane oxygenation; ARF, acute renal failure; ARDS, acute respiratory distress; R/O, rule out; PTE, pulmonary thromboembolism; VT, ventricular tachycardia; AMI, acute myocardial infarction; STEMI, ST elevation myocardial infarction; DIC, disseminated intravascular coagulation; TPL, transplantation.

bumin during ECMO were statistically insignificant. Further, mean arterial pressure and the amount of blood transfusion were not significant as well. Base excess, flow of ECMO, inotropic score, and changes in the level of serum creatinine did not show any statistical differences. Eleven cases of suc-

cessful weaning groups are showed lower AKIN$_{48\text{-hour}}$ stage, but no statistical significance (Table 3).

SAPS and SOFA scores were not matched with prognosis of ECMO. There were no statistical significant factors except myocarditis. We assumed that there were some hidden fac-

tors, which were showed no significant p-value due to small number of total cases. So we applied area under receiver operating characteristics curve, to find that factors. The level of hemoglobin at 24 hours after ECMO, and base excess at 48 hours after ECMO were showed more than 0.7 (Table 4). If the number of cases is enough, these factors may be considered as cut off values. Although successful weaning of ECMO, 6 patients died. Brief explanation about them is presented as Table 5.

DISCUSSION

Due to myocardial destruction and remodeling, persistent ventricular dysfunction and dilated cardiomyopathy occurs frequently in myocarditis. Insufficient drainage of right ventricular and bronchial circulation will lead to left ventricular (LV) distension. LV distension interferes with myocardial rest and thus greatly imposes impact on influencing the prognosis. Therefore, LV venting may be helpful in patients with myocarditis during ECMO. In Seoul National University Bundang Hospital, myocarditis patients did not received LV venting for various reasons. So weaning failures from ECMO in these patients might be result from this. Hemorrhage related with the use of anticoagulants and the formation of thrombus are typical complications that may be occur during ECMO. Aside from this, long term management may cause severe damage for organs and thus leading to poor prognosis. Leukocytes, thrombocytes, and complements are activated by ECMO. Acute inflammatory-like reaction can be introduced during the first 24 to 48 hours by the secretion of cytokines, which may cause capillary leakage and thus lead to intravascular volume depletion [5,6]. In addition, it is known that the long instillation of ECMO can cause problems, such as hemolysis, and lead to organ damages. Lin et al. [7] reported that the change in creatinine levels and hour urine during ECMO is closely related to the prognosis. A few years later, he reported that AKIN scores at the time of 48 hours after initiation of ECMO was close related with the prognosis [8]. In this study, the relationship between AKIN score and ECMO weaning was not statistically confirmed. However, there were tendency of less severe degree of metabolic acidosis, slightly higher flow of ECMO, and less inotropic score

and changes in the level of serum creatinine in the successful weaning group. It is a likely possibility that these results arose due to small sample size of patients. If larger number of ECMO patients, the outcome may differ.

Recently, new ECMO equipments are being introduced to reduce the occurrence of hemolysis. Studies regarding these devices and its impact on lowering kidney injuries may be needed. The degree of acidosis 48 hours after initiation of ECMO may reflect the degree of renal insufficiency. The hemoglobin level at the time of 24 hours after initiation of ECMO, regardless of the amounts of transfusion, may be the possible prognostic factor, and degree of acidosis at 48 hours after initiation of ECMO is also.

Maybe due to the small population of the sample size, meaningful factors related with prognosis were not found in this study. The increase in the duration of ECMO causes organ dysfunction and will provoke a change in the hemoglobin level. In addition, a progression of acidosis will adversely affect the prognosis of the patients. From this perspective, the result of this study may show some relationship between factors and prognosis. With reduction of hemolysis and acidosis, the renal injury will occur less frequently and thus, will result in a better prognosis of ECMO patients.

The first limitation of this present study was that number of the patients enrolled in the study was too small to prove or disprove the existing hypothesis. This could lead to selection bias. Secondly, the comparison was not possible between the LV venting group in patients with myocarditis and no venting. It is not possible to differentiate whether myocarditis itself is a poor prognosis factor, or LV venting. However, if the situation of myocarditis is considered, the possibility of the latter is more likely [9,10].

CONCLUSION

This study showed that the hemoglobin levels of 24 hours after ECMO and degrees of acidosis 48 after initiation of ECMO are thought as prognostic factors. And patients with myocarditis had poor prognosis in our cases. There was no statistical relation between ECMO and renal injury. Further study may be needed in the future.

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