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Venovenous Extracorporeal Membrane Oxygenation for Postoperative Acute Respiratory Distress Syndrome

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Background: Extracorporeal membrane oxygenation (ECMO) has recently attracted interest as a treatment for severe acute respiratory distress syndrome (ARDS). However, the outcomes of this procedure in post-surgical settings have not yet been characterized. In this study, we evaluated the outcomes of ECMO in patients with severe postoperative ARDS. ***Methods:*** From January 2007 to December 2012, a total of 69 patients (aged 58.3±11.5 years, 23 females) who underwent venovenous ECMO to treat severe postoperative ARDS were reviewed. Of these patients, 22 (31.9%) had undergone cardiothoracic surgery, 32 (46.4%) had undergone liver transplantation, and 15 (21.7%) had undergone other procedures. ***Results:*** Thirty-four patients (49.3%) were successfully weaned from ECMO, while the other 35 patients (50.7%) died on ECMO support. Among the 34 patients who were successfully weaned from ECMO, 21 patients (30.4%) eventually died before discharge from the hospital, resulting in 13 hospital survivors (18.8%). Multivariable analysis showed that the duration of pre-ECMO ventilation was a significant independent predictor of death (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.29 to 3.90; p=0.004), whereas the concomitant use of continuous venovenous hemodialysis (CVVHD) was associated with improved survival (OR, 0.55; 95% CI, 0.31 to 0.97; p=0.038). ***Conclusion:*** Although the overall survival rate of patients treated with ECMO for postoperative ARDS was unfavorable, ECMO offered an invaluable opportunity for survival to patients who would not have been expected to survive using conventional therapy. CVVHD may be beneficial in improving the outcomes of such patients, whereas a prolonged duration of pre-ECMO ventilator support was associated with poor survival.

Key words: 1. Acute respiratory distress syndrome (ARDS)
2. Extracorporeal membrane oxygenation
3. Survival
4. Prognosis

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by the rapid onset of hypoxemia caused by the combination of acute and persistent pulmonary inflammation with increased vascular permeability. The overall in-hospital mortality rate for ARDS has been reported as 40% to 60% in published case series [1-3]. Since the mortality rate of severe ARDS is still higher, even when state-of-the-art medical treatment is deployed, extracorporeal membrane oxygenation has emerged as a promising technique that allows patients to circumvent the period of profound hypoxemia and hypercarbia associated with severe ARDS and increases the likelihood of survival.

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In a large multicenter randomized trial, a significant survival benefit was observed when Extracorporeal membrane oxygenation (ECMO) support was used for the treatment of patients with ARDS, compared to conventional management [4]. Since then, the role of ECMO in treating respiratory failure in various clinical settings has been discussed worldwide and recognized to be an important issue. According to recent registry data from the Extracorporeal Life Support Organization, the worldwide usage of venovenous ECMO (VV-ECMO) to treat severe ARDS has increased substantially, with an early survival rate that has been reported to be approximately 50% [5].

Meanwhile, pulmonary complications following major surgery are known to be the leading cause of early post-surgical mortality, and survival is rarely expected if ARDS occurs in such patients [6]. In light of its potential to improve treatment outcomes, the role of ECMO in this subset of patients has attracted considerable attention and been debated among practicing physicians. A review of the literature, however, found little research on the use of ECMO for the treatment of postoperative ARDS. In this study, we sought to analyze the outcomes of VV-ECMO support in patients with severe ARDS who had undergone major surgery under general anesthesia.

METHODS

1) Patients

All patients undergoing VV-ECMO are prospectively registered in a database at Asan Medical Center, Seoul, Korea, in which baseline patient characteristics, details of ECMO management, and in-hospital outcomes were recorded. From January 2007 to December 2012, 119 patients received VV-ECMO for acute respiratory support. Sixty-nine of these patients (mean age, 58.3±11.5 years; 23 females) who underwent ECMO due to severe postoperative ARDS were chosen for inclusion in this study.

We used the Murray scoring system to evaluate the severity of ARDS [2]. The Murray scoring system results in a score from 0 to 4, according to the severity of the score assigned for each of the following criteria: hypoxemia, respiratory system compliance, chest radiographic findings, and level of positive end-expiratory pressure. The final score is obtained by dividing the total score by the number of criteria that were used. A score of 0 indicates no lung injury, a score of 1–2.5 indicates mild to moderate lung injury, and a score >2.5 indicates the presence of ARDS.

We also used the Sequential Organ Failure Assessment (SOFA) score, which is a scoring system that determines the extent of an individual's organ function in the intensive care unit [7]. The score is based on six different subscores, with a separate subscore assigned for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. Both the mean and highest SOFA scores of a given patient can predict his or her outcome. An increase in the SOFA score during the first 24 to 48 hours in the intensive care unit predicts a mortality rate of 50% to 95%. Scores <9 predict a mortality rate of 33%, while scores >11 predict a mortality rate close to or above 95%.

2) Extracorporeal membrane oxygenation procedure and management

ECMO was performed in the intensive care unit in all cases. After a 150 U/kg intravenous bolus of heparin, ECMO cannulae were placed in the right atrium and inferior vena cava through both femoral veins.

The protocol for managing ECMO included maintaining blood flow to meet the goal of arterial oxygen saturation $>85\%$. Standard heparin was given by continuous infusion at a rate titrated to maintain the desired whole blood activated clotting time of 160 to 180 seconds. The ECMO flow rate was adjusted to maintain gas exchange and hemodynamic stability with the ventilator set to rest. The timing of ECMO weaning was determined based on the clinical judgment of the attending physicians considering clinical parameters such as gas exchange profiles, radiologic improvements in the lungs, and the patient's general condition. In general, patients were weaned from ECMO when they had adequate oxygenation, as proven by an arterial oxygen saturation reading of 90% with a fractional inspired oxygen concentration ≤ 0.5. When lung function had improved, patients were weaned from ECMO at moderate ventilator settings and decannulated if gas exchange was considered to be adequate. Successful weaning was defined as separation from ECMO without mortality over a 24-hour period, without resumption of ECMO [8].

Table 1. Characteristics of patients

Characteristic	Total (n=69)	Survivors (n=13)	Non-survivors (n=56)	p-value
Age (yr)	58.3±11.5	54.3±11.1	59.3±11.5	0.228
Male/female	43/23	8/5	38/18	0.663
Weight (kg)	62.2±12.4	61.2±12.4	62.5±12.4	0.427
ECMO duration (hr)	333.2±1,004.3	896.5±1,930.5	202.3±583.9	0.411
Ventilator mode (number of patients)	18/51	1/12	17/39	0.094
PaO_2/FiO_2 ratio	60.9±20.6	58.9±14.5	61.3±21.9	0.435
Pre-ECMO ventilator duration (day)	9.2±10.2	5.8±10.5	10.0±10.1	0.813
Pre-ECMO ventilator settings				
FiO_2	0.96±0.12	1.00±.00	0.96±0.13	0.936
Tidal volume (mL)	452.8±139.9	513.2±177.4	438.8±127.6	
Peak inspiratory pressure (cm H_2O)	24.0±7.9	17.5±5.1	25.4±7.7	0.663
Positive end expiratory pressure (cm H_2O)	7.7±4.2	8.5±4.4	7.5±4.1	0.511
Pre-ECMO arterial blood gas				
PaO_2 (mmHg)	56.9±14.7	58.3±14.2	56.5±14.9	0.358
Partial pressure of arterial carbon dioxide (mmHg)	55.9±19.0	41.9±11.1	59.1±19.0	0.667
pH	7.26±0.12	7.31±0.09	7.25±0.13	0.716
Arterial oxygen saturation (%)	79.7±14.4	84.1±10.4	78.7±15.1	0.687
Lactic acid (mmol/L)	4.6±4.4	4.3±4.0	4.6±4.6	0.683
Creatinine (mg/dL)	1.44±0.95	1.55±1.09	1.41±0.92	0.643
Type of surgery				0.050
Cardiac surgery	8 (11.6)	1 (7.7)	7 (12.5)	
Thoracic surgery	14 (20.3)	1 (7.7)	13 (23.2)	
Liver transplantation	32 (46.4)	5 (38.5)	27 (48.2)	
Other	15 (21.7)	6 (46.1)	9 (16.1)	
Continuous venovenous hemodialysis	47 (68.1)	11 (84.6)	36 (64.3)	0.137

Values are presented as mean±standard deviation or number (%).
ECMO, extracorporeal membrane oxygenation; PaO_2, partial pressure of arterial oxygen; FiO_2, fractional inspired oxygen concentration.

Table 2. Multivariable logistic regression analysis for mortality

Variable	Odds ratio	95% confidence interval	p-value
Shock	1.816	1.058–3.117	0.030
Use of continuous venovenous hemodialysis	0.548	0.310–0.968	0.038
Mechanical ventilation duration (>5 days)	2.251	1.299–3.902	0.004
Sequential Organ Failure Assessment score (using increments of 1)	1.106	1.006–1.216	0.038
Pre-extracorporeal membrane oxygenation arterial pH	0.168	0.020–1.429	0.102

3) Statistical analysis

Categorical variables, presented as frequencies and percentages, were compared using the chi-square test or the Fisher's exact test. Continuous variables, expressed as mean±standard deviation or median with range, were compared using the Student unpaired t-test or the Mann–Whitney U-test. Kaplan–Meier curves were used to express the cumulative incidence of death, and log-rank tests were used to compare between-group differences in mortality rates. In the multivariate analysis of mortality rates, logistic regression models were used to determine risk factors for death and adverse events. The variables listed in Tables 1 and 2 were evaluated in the models, and those with a p-value ≤0.20 in the univariate analysis were candidates for the multivariate models. The multivariate analysis employed a backward elimination technique, and on-

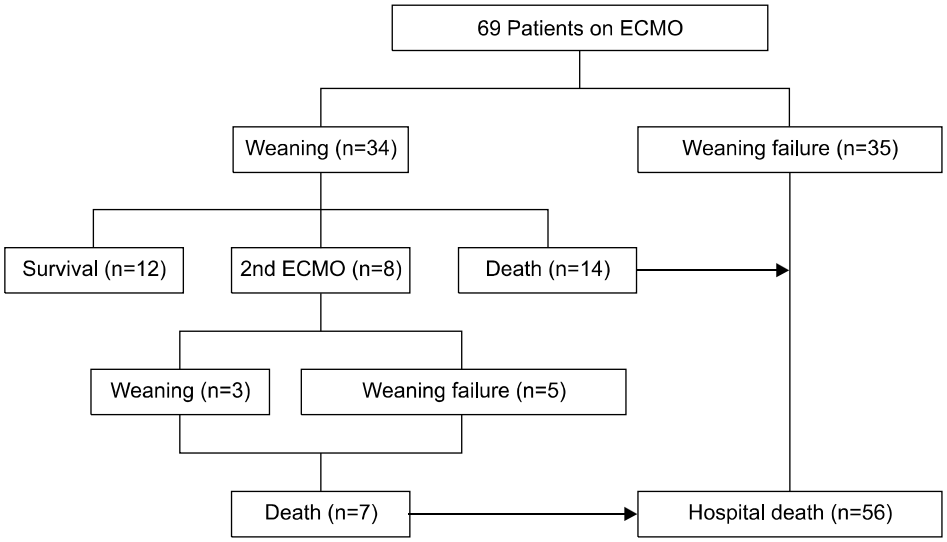

Fig. 1. Flow chart of in-hospital outcomes. ECMO, extracorporeal membrane oxygenation.

ly variables with a p-value <0.10 were used in the final model. The final model was validated with 1,000 bootstrap samples. IBM SPSS software ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis.

RESULTS

1) Baseline characteristics

The baseline demographic and clinical characteristics of the patients are presented in Table 1. The median age was 58.3 years (range, 28.0 to 76.0 years), and the median body weight was 62.2 kg (range, 37.5 to 100.0 kg). Twenty-two patients (31.9%) had undergone cardiothoracic surgery, 32 patients (46.4%) had undergone liver transplantation, and 15 patients (21.7%) had undergone gynecological surgery, kidney transplantation, colon resection, or another procedure. Fifty-one (73%) patients were on mechanical ventilation using the pressure control mode before ECMO support. The median ventilator duration before ECMO support was 9.2 days (range 0.0 to 39.0 days). The median Murray score was 2.88 (range, 2.3 to 4.0).

2) In-hospital outcomes and predictors of mortality

Thirty-five patients (50.7%) died on ECMO support and 34 patients (49.3%) were successfully weaned from ECMO. Of the 34 patients who were successfully weaned from ECMO, 14 patients died in the hospital without a second period of ECMO support. Another eight patients (11.6%) underwent a second ECMO procedure; however, seven of these patients eventually died in the hospital, with only one survivor. The other 12 patients who were successfully weaned survived and were discharged from the hospital, resulting in a total of 13 hospital survivors (18.8%). A flow chart of the outcomes is presented in Fig. 1.

Of the survivors, four patients (30.8%) required a conversion from VV-ECMO to venoarterial ECMO before weaning, in order to provide temporary hemodynamic support. Of the non-survivors, 15 patients (36.6%) required conversion to venoarterial ECMO. The mean duration of ECMO was 230.1±149.0 hours (range, 30.8 to 597.0 hours) in survivors, and 172.4±182.5 hours (range, 9.0 to 717.8 hours) in non-survivors (p=0.044).

A comparison of the demographic profiles of survivors and non-survivors is presented in Table 1, indicating no significant differences in age, the pre-ECMO ratio of the partial pressure of arterial oxygen to the fractional inspired oxygen concentration, pre-ECMO ventilator duration, renal function, or Murray and SOFA scores. However, patients who had undergone cardiothoracic surgery (9.1%) or liver transplantation (15.6%) showed significantly lower survival rates than those who had undergone other operations (40.0%, p=0.05).

Multivariate analysis showed that shock, a pre-ECMO ventilation duration of more than five days, and a high SOFA score were significant and independent risk factors for mortal-

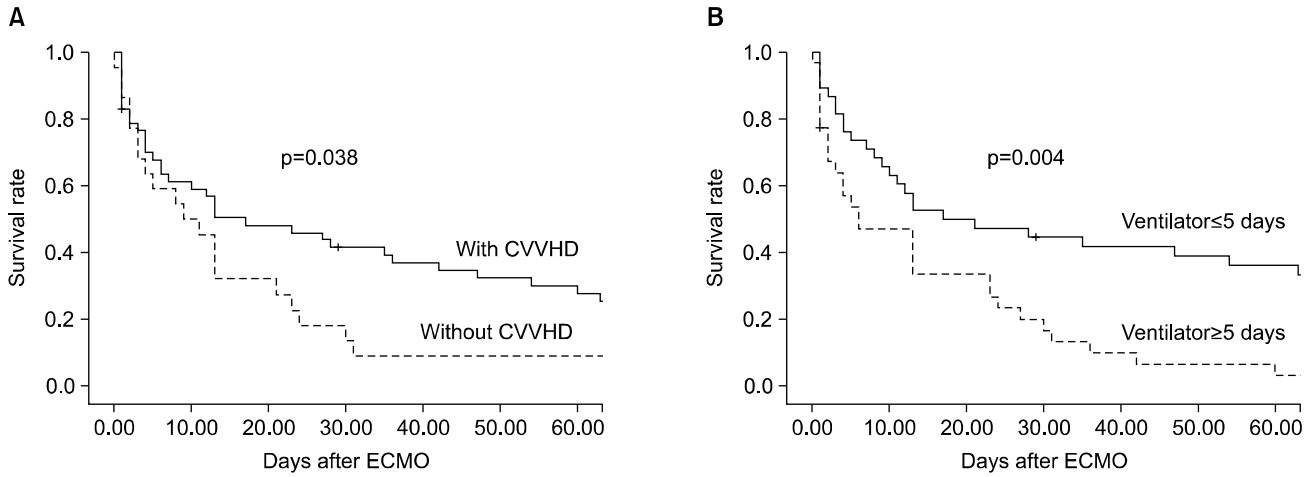

Fig. 2. Kaplan-Meier curves for survival estimates, presenting the differences in survival rates according to (A) the use of CVVHD and (B) the duration of mechanical ventilation before ECMO. CVVHD, continuous venovenous hemodialysis; ECMO, extracorporeal membrane oxygenation.

ity, while the concomitant use of continuous venovenous hemodialysis (CVVHD) was found to be protective against mortality (Table 2). The Kaplan-Meier curves showed a remarkable difference in survival rate depending on the use of CVVHD (Fig. 2A) and the pre-ECMO ventilation duration (Fig. 2B).

DISCUSSION

ECMO has been accepted as a standard treatment for severe respiratory failure in newborn and pediatric patients who fail to respond to conventional therapy [8]. For adult patients with acute respiratory failure, ECMO support has shown to improve survival rates in some subsets of patients, but the generalized application of this treatment in a full range of clinical settings remains controversial.

We have not generally performed ECMO for moderately severe ARDS in cases where conventional therapy may still offer acceptable gas exchange profiles. The benefit versus risk of ECMO for moderate ARDS is still controversial and has not been well evaluated to date. The fact that this issue remains unresolved led us to adopt relatively strict indications for using ECMO to treat ARDS in our center, which might have led to the relatively poor outcomes that we observed in patients treated with ECMO.

In the present study, the survival rate of patients treated with VV-ECMO for severe postoperative ARDS was only 18.8%, which reflects very unfavorable outcomes. The cause of death in all patients was sepsis, similar to what occurs in the course of ARDS. However, postoperative ARDS tends to be faster and have a more aggressive progression than ARDS more generally. Nevertheless, this figure should not be interpreted as discouraging the use of ECMO to treat postoperative ARDS, because this result may be explained by the unique characteristics of patients population in Asan Medical Center, Seoul, Korea, which handles a high volume of very critical surgical patients. For instance, most patients included in this study had undergone cardiothoracic surgery (31.9%) and liver transplantation (46.4%), and therefore had expected surgical risks much higher than patients who had undergone operations involving other organ systems. The hospital survival rates in the present study were 9.1% (2/22) for patients who had undergone cardiothoracic surgery, 15.6% (5/32) for patients who had undergone liver transplantation, and 40.0% (6/15) for patients who had undergone other operations (p=0.05). Although the multivariable analysis did not show that the type of surgery was an independent predictor of mortality, we believe that this is due to statistical overfitting, in which too many variables are incorporated in modeling a relatively small sample. Therefore, studies with larger sample sizes should investigate whether surgery type affects the outcomes of ECMO used to treat postoperative ARDS.

Acute kidney injury is a well-known independent risk factor for increased in-hospital mortality in pediatric patients requiring ECMO [9]. In addition, fluid overload during ECMO support has been associated with an increased risk of mortality [10,11]. The basic pathophysiology of postoperative ARDS involves an acute inflammatory cascade that can lead to pulmonary edema. Cellular damage caused by progressive and refractory hypoxemia subsequently increases the permeability of the pulmonary capillaries, leading to the eventual accumulation of intravascular fluid in the interstitial space [12]. Extracorporeal circulation using ECMO may further aggravate interstitial edema via an inflammatory foreign-body reaction. In this context, CVVHD may play a beneficial role in regulating body fluids during ECMO support in patients with ARDS [13]. The use of CVVHD is expected to decrease fluid overload, remove inflammatory mediators, control electrolyte abnormalities, and decrease the use of intravenous diuretics [14,15], and we propose that these effects may explain the finding in the present study that concomitant CVVHD has a beneficial effect on mortality rates.

This study has several limitations. First, this study is subject to the limitations inherent to retrospective analyses of observational data. Most patients enrolled in this study had very severe postoperative ARDS and were not expected to survive with conventional therapy. This selection bias means that the study results may not be generalizable to patients with milder forms of ARDS. Moreover, the relatively small number of patients in this study did not allow strong statistical adjustment. Therefore, studies with larger populations are needed in future research.

In conclusion, very critical patients with severe postoperative ARDS who were treated with ECMO were evaluated in this study. Although the early survival rates were unfavorable (18.8%), ECMO offered an invaluable opportunity for survival to patients who would not have been expected to survive using conventional therapy. The concomitant use of CVVHD may improve outcomes, whereas the duration of pre-ECMO mechanical ventilation was associated with poor survival in these patients.

CONFLICT OF INTEREST

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

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