Original Article

Evaluation of Prognosis in Patients with Respiratory Failure Requiring Venovenous Extracorporeal Membrane Oxygenation (ECMO)

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Purpose: In this study, we analyzed the respiratory status and the prognosis of patients, including adults with acute respiratory failure requiring venovenous extracorporeal membrane oxygenation (VV ECMO) to maintain respiratory status. We then evaluated the differences between patients who could be removed from VV ECMO and those who could not.
Patients and Methods: From January 2003 to December 2008, eleven patients in our hospital required VV ECMO for severe acute respiratory failure. All 11 had severe acute respiratory distress syndrome. The age of the patients was 52 ± 24 (range; 8–86) years, and the male/female ratio was 8/3. The acute physiology and chronic health evaluation II (APACHE II) score, ECMO flow, and respiratory parameters, such as PaO_2/FiO_2 (P/F ratio), pulmonary compliance, and Lung Injury Score (LIS) before and after the introduction of ECMO, were compared among patients in whom ECMO could or could not be removed.
Results: ECMO could be removed from six patients (55%, group A), but in five (45%, group B) could not. The duration of ECMO support was significantly shorter in group A than in group B (111 ± 68 hr vs. 380 ± 233 hr, p = 0.011). The pre-ECMO ventilator time was shorter in group A than in group B. Significant differences were found between the two groups in the P/F ratio and LIS from pre-ECMO introduction to 72 hours after. ECMO flow in group A could be weaned for 48 hours after introduction, significantly different compared with group B.
Conclusion: The early introduction of ECMO may be desirable if the causes of respiratory failure are recoverable. It is presumed that VV ECMO removal will be difficult if the ECMO flow cannot be weaned within 48 hours after ECMO introduction in patients with severe respiratory failure. (Ann Thorac Cardiovasc Surg 2010; 16: 156–162)

Key words: respiratory failure, acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO), venovenous

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Introduction

The aims of the treatment of acute respiratory failure are maintenance of oxygenation and CO_2 removal while avoiding ventilator-induced lung injury related mainly to barotrauma, local and systemic effects of the release of inflammatory mediators, and oxygenation toxicity.[1)] Extracorporeal membrane oxygenation (ECMO) is a

Table 1. Backgrounds of patients

No.	Age	Gender	Underlying diagnosis	The cause of respiratory failure	ECMO removal
1	67	M	Esophageal cancer(after esophagectomy)	Pneumonia (P. A.)	Yes (group A)
2	86	M	Phlegmon of right cheek	Pneumonia (P. A.)	Yes (group A)
3	8	F	AML (after BMT)	Diffuse alveolar hemorrhage	Yes (group A)
4	55	M	Pulmonary fibrosis	Pulmonary fibrosis	Yes (group A)
5	50	M	Tracheal burn	Tracheal burn	Yes (group A)
6	72	M	Aspiration pneumonia	Aspiration pneumonia	Yes (group A)
7	61	F	Esophageal cancer (after esophagectomy)	Pneumonia (P.A.)	No (group B)
8	57	M	Post LDLTx	Pneumonia (P. A.)	No (group B)
9	16	F	ALL (after BMT)	PCP	No (group B)
10	14	M	ALL (after BMT)	Pneumonia (P.A.) PCP	No (group B)
11	79	M	Cerebral infarction	Aspiration pneumonia	No (group B)

P.A., Pseudomonas aeruginosa; AML, acute myelogenous leukemia; BMT, bone marrow transplantation; LDLTx, living donor liver transplantation; ALL, Acute lymphoid leukemia; PCP, pneumocystis carini pneumonia.

technique using capillary or membrane oxygenators for gas exchange, thereby providing life support should the lungs fail and become unable to maintain sufficient oxygenation of the body's organ systems.[2] The use of ECMO is an option in patients who have acute severe respiratory failure and who are failing all advanced modes of mechanical ventilation, such as limitation of end-inspiratory plateau pressure and tidal volume, inverse ratio ventilation, titration of positive end-expiratory pressure (PEEP) by SvO_2, permissive hypercapnea, limitation of FiO_2, nitric oxide inhalation, and surfactant replacement.[1,3] ECMO is a proven modality for the treatment of severe respiratory failure in neonates.[4,5] However, its usefulness in adults remains controversial.[3,6]

In this study, we analyzed the prognosis of patients with acute respiratory failure requiring venovenous (VV) ECMO and evaluated the differences between patients who could be removed from VV ECMO and those who could not.

Patients and Methods

From January 2003 to December 2008, eleven patients required VV ECMO for severe acute respiratory failure in the intensive care unit (ICU) of Gunma University Hospital. The underlying diagnoses of the patients are shown in Table 1. All 11 had severe acute respiratory distress syndrome (ARDS). The age of the patients was 52 ± 24 (range, 8–86) yr, and the male/female ratio was 8/3.

Indication for ECMO

Patients with acute, reversible, life-threatening respiratory failure unresponsive to conventional therapy were candidates for VV ECMO. Specifically, the criteria to receive VV ECMO in our hospital were as follows: (1) PaO_2/FiO_2 (P/F ratio) < 100 mmHg; (2) uncontrollable respiratory acidosis resulting from severe hypercapnea with conventional ventilator strategies (pH <7.2); or (3) pulmonary compliance < 30 ml/cmH_2O. Patients with both respiratory failure and heart failure who required venoarterial ECMO were excluded in this study.

ECMO method

The ECMO system comprised a hollow-fiber microporous membrane oxygenator, a heat exchanger, a centrifugal pump, arterial and venous cannulae, and standard 3/8-inch tubing. The blood-contact surfaces of these components were heparin-coated. ECMO was established with venous drainage (19.5 Fr or 21 Fr) from the femoral vein (the tip of the tube was placed in the right atrium), and arterialized blood was returned to another side of the femoral vein using a 15 Fr or 16.5 Fr arterial cannula (Fig. 1). In recent practice, we have used a Capiox SP Pump Controller Sp-101 and a Capiox circuit (Terumo Co., Tokyo, Japan). ECMO flow was initially maintained in the range of 1.0 to 2.0 L/min/m^2, and the activated clotting time was maintained at 150–250 seconds with the administration of nafamostat mesylate, a potent antiplatelet agent, during ECMO. Antibiotics were administered only when microbial infections were proven.

When lung function improved, we attempted to wean the patient from ECMO by gradually reducing the ECMO flow, and ECMO was removed if gas exchange was adequate with an ECMO flow rate of less than 1.0 L/min/m^2 and with moderate ventilator settings (FiO_2 < 0.6, peak inspiratory pressure < 30 cmH_2O, PEEP < 15

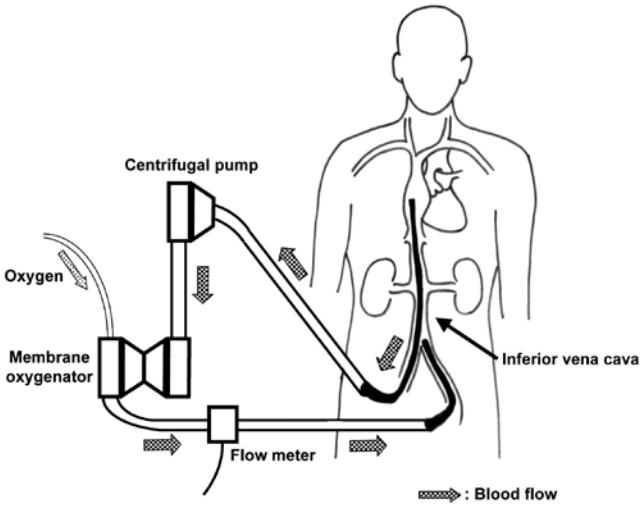

Fig. 1. A schema of the VV ECMO method.

cmH_2O, and respiratory rate < 40/min) for at least a few hours. After successful weaning from ECMO, every patient remained on mechanical ventilation until standard extubation criteria were met. They were discharged from the ICU when they were determined stable after release from mechanical ventilation.

In this study, the acute physiology and chronic health evaluation II (APACHE II) score (which shows a patient's general condition), ECMO flow, and respiratory parameters such as P/F ratio, pulmonary compliance, and Lung Injury Score (LIS) before and after the introduction of ECMO, were compared among patients in whom ECMO could be removed and in whom ECMO could not be removed.

Statistical analysis

All results were expressed as the mean and the standard deviation (SD). Statistical comparisons were made using the Mann-Whitney U test and repeated measure analysis of variance (ANOVA), followed by Fisher's protected least significant difference. StatView software version 5.0 (Abacus, Berkeley, CA) was used for statistical analyses. A P value of less than 0.05 was interpreted as being statistically significant.

Results

The mean lengths of ECMO support time, mechanical ventilation time, and ICU stay for the 11 patients were 233 ± 208 (47–749) hours, 644 ± 581 (97–1832) hours, and 30 ± 22 (6–74) days, respectively. VV ECMO could be removed from 6 patients (55%, group A). Among 6 patients in group A, 4 (36% of all 11 patients) could be discharged from ICU, and 2 patients died in the ICU resulting from multiple organ failure (MOF). On the other hand, ECMO could not be removed from 5 patients (45%, group B). There were no significant differences in changes of systolic blood pressure or heart rate between the two groups during ECMO support (Fig. 2). In group B, all five patients died as a result of MOF.

As shown in Table 2, the duration of ECMO support was significantly ($p = 0.011$) shorter in group A than in group B. The pre-ECMO ventilator time (from the start of mechanical ventilator support to ECMO introduction) was shorter in group A than in group B without a significant difference. The total mechanical ventilation time and the length of ICU stay were longer in group A than in group B. It was believed that long-term mechanical ventilator support and intensive care were required for respiratory management after ECMO removal in group A. The rate of use of renal replacement therapy (RRT, such as hemodialysis and/or continuous hemodiafiltration) before ECMO introduction was higher in group B than in group A, but the difference was insignificant (Table 2).

As shown in Fig. 3a, there were no significant differences in APACHE II before and after ECMO introduction between the two groups. APACHE II score in group A was gradually improved; however, in group B it did not change until 72 hr after ECMO introduction. The pH levels in arterial blood were improved after ECMO introduction in both groups, and there were no

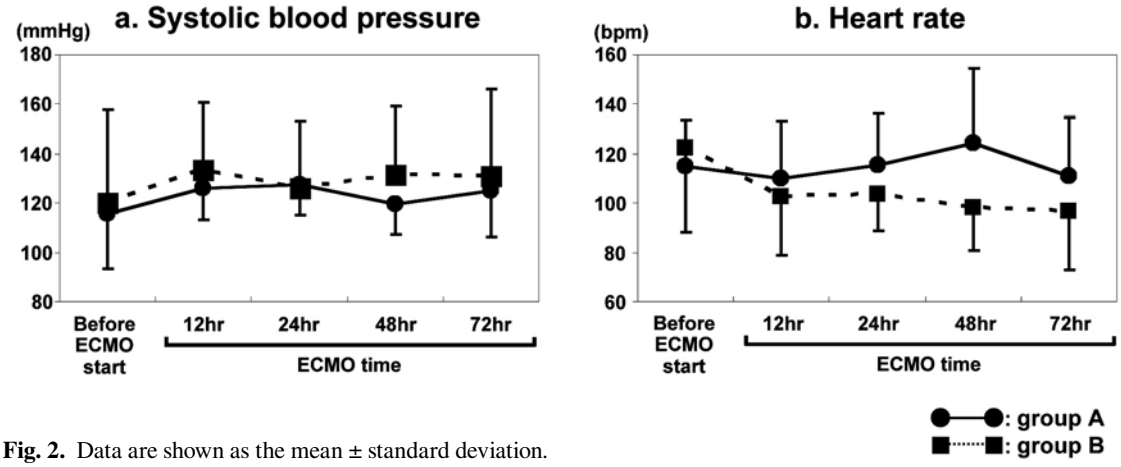

Fig. 2. Data are shown as the mean ± standard deviation.

Table 2. Comparisons of clinical results between the two groups

	group A	group B	p value
The duration of ECMO support (hr)	111 ± 58	380 ± 233	0.011
The total mechanical ventilation time (hr)	682 ± 793	599 ± 233	0.465
The pre-ECMO ventilator time (hr)	157 ± 353	216 ± 178	0.100
The length of stay in the ICU (days)	32 ± 30	29 ± 10	0.465
The use of RRT before ECMO introduction	0%	20% (1/5)	0.273

RRT, renal replacement therapy.

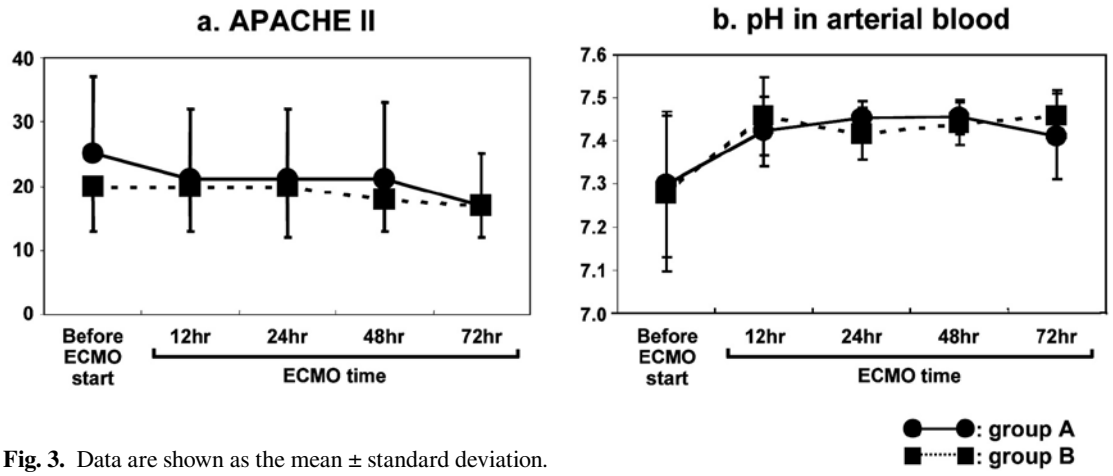

Fig. 3. Data are shown as the mean ± standard deviation.

significant differences in the pH levels between the two groups (Fig. 3b).

P/F ratio in group A was significantly ($p < 0.05$) better than in group B before ECMO introduction (Fig. 4a), and in group A it was improved after ECMO introduction, with significant ($p < 0.05$) differences in comparison to group B (Fig. 4a). As shown in Fig. 4b, pulmonary compliance prior to ECMO use was impaired in both groups, and this parameter was almost the same in the two groups until 24 hr after ECMO use. However, pulmonary compliance was gradually improved in group A, and it was better than in group B during the 48 hr after ECMO introduction. On the other hand, an improvement of pulmonary compliance was not found in group B.

LIS in group A was significantly ($p < 0.05$) better than in group B before ECMO introduction (Fig. 5a). LIS in group A was gradually improved after ECMO introduction, with significant ($p < 0.05$) differences in comparison to

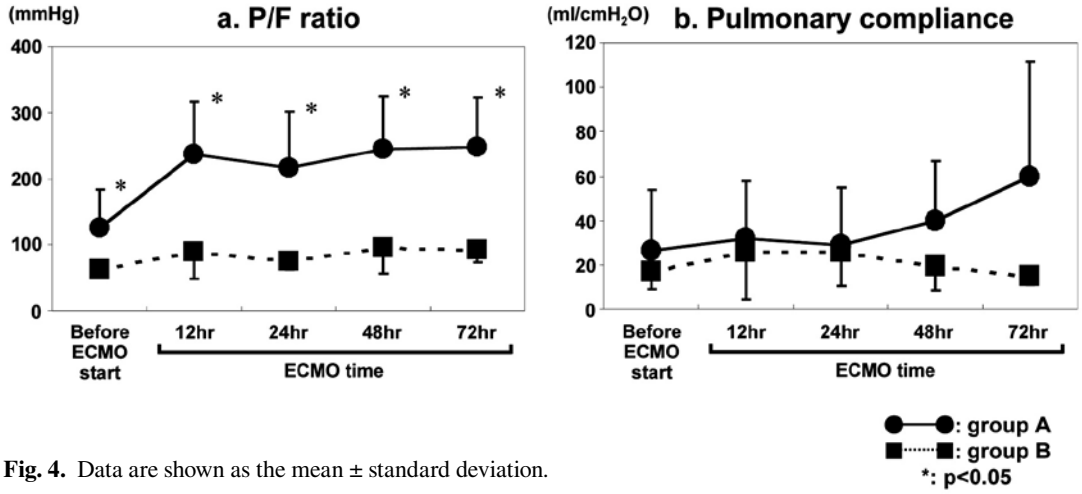

Fig. 4. Data are shown as the mean ± standard deviation.

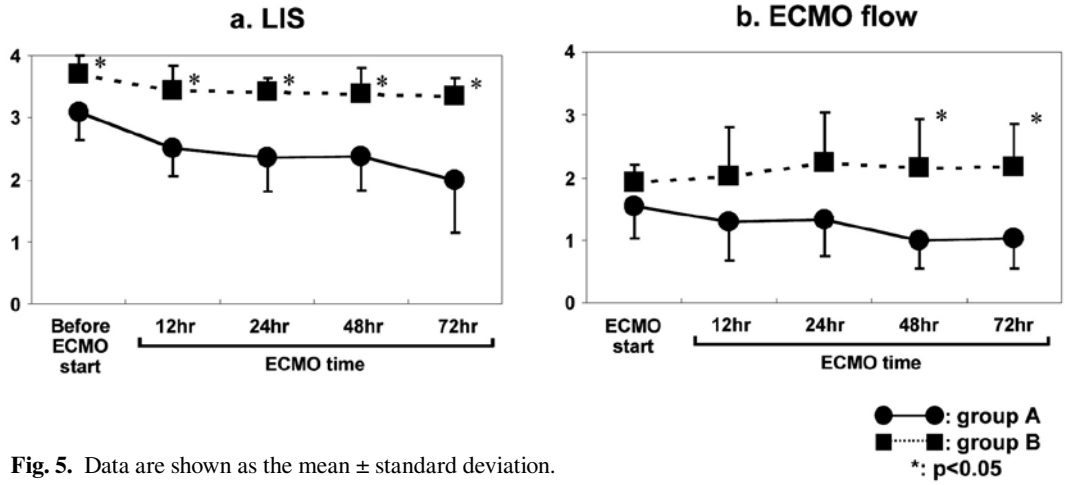

Fig. 5. Data are shown as the mean ± standard deviation.

group B; however, an improvement of LIS was not found in group B.

As shown in Fig 5b, there was no significant difference in ECMO flow between the two groups when ECMO was started. The ECMO flow in group A could be gradually weaned after ECMO introduction with significant ($p < 0.05$) differences at 48 and 72 hr after ECMO use. However, the ECMO flow in group B could not be weaned until 72 hr after ECMO introduction.

There were no complications of anticoagulation therapy by administration of nafamostat mesilate in either group during ECMO support.

Discussion

ECMO has an established place in the treatment of acute cardiopulmonary failure in children based on more than 25 years of accumulated clinical experience.[7,8] The largest number of patients who received ECMO support is documented in the Extracorporeal Life Support Organization (ELSO) Registry at the University of Michigan in Ann Arbor. The ELSO database now contains outcome data on over 20,000 patients with survival rates varying from more than 80% in neonates to 40%–50% in older children and adults.[7] A randomized study in the United Kingdom showed a superiority of ECMO in neonates with severe respiratory failure compared to conventional ventilation.[9] ECMO has also been used for the treatment of adults with severe respiratory failure since the 1970s, and two randomized trials showed no superiority of ECMO in comparison to conventional treatment.[10,11] However, there has been an encouraging experience of the successful use of ECMO as an effective therapy in adults with severe respiratory failure. Linden et al.[12]

reported that a high survival rate of 76% could be obtained in adult patients with severe ARDS using ECMO and pressure-supported ventilation with minimal sedation. Hemmila et al.[13] insisted that extracorporeal life support for severe ARDS in adults was a successful therapeutic option in patients who did not respond to conventional mechanical ventilator strategies. It has been well documented that ECMO use leads to a positive impact on outcomes following graft failure after lung transplantation.[14,15] Moreover, ECMO is suitable for ARDS in adults with burn injuries[16] and trauma.[17] The usefulness of VV ECMO in patients with severe hypoxia based on empyema has been also reported.[18]

In this study, we analyzed the respiratory status and the prognosis of patients with acute respiratory failure requiring VV ECMO for respiratory support in our hospital. ECMO could be removed in 6 patients (55%), and 4 of these patients (36%) could be transferred to the normal ward. The ECMO support time in group A was significantly shorter than in group B, and the pre-ECMO ventilator time was also shorter in group A than in group B. It had been reported that the ECMO support time and pre-ECMO ventilator time were significantly shorter in survivors than in nonsurvivors among adults with respiratory failure requiring ECMO.[13] There were no significant differences in APACHE II scores between the two groups. The P/F ratio and LIS before ECMO introduction were significantly better in group A than in group B, and these parameters in group A were also significantly better than in group B after ECMO introduction. Those results showed that respiratory condition was severer in group B than in group A, though general status except for respiratory condition was almost the same. Moreover, ECMO flow in group A was gradually weaned with significant differences at 48 and 72 hours after ECMO introduction. Taking the results of previous studies and our results into consideration, we presumed that the most important factors for weaning from ECMO are wasting no time in ECMO introduction and the improvement of P/F ratio, pulmonary compliance, and LIS until 72 hours after ECMO introduction. The following recommendations on VV ECMO can be made: (1) it might be desirable to introduce ECMO as early as possible prior to the occurrence of lung injury because of long-term mechanical ventilation support if the cause of respiratory failure is recoverable; (2) after ECMO introduction, the P/F ratio, pulmonary compliance, and LIS should be periodically measured and calculated as parameters of pulmonary function, and ECMO may be removed in patients in whom ECMO flow can be gradually weaned by 48 hours after ECMO use. It may be difficult to remove ECMO from patients without those findings. Hemmila et al.[13] reported that multivariate logistic regression analysis identified the following pre-ECMO variables as significant independent predictors of survival: age, gender, pH, P/F ratio, and number of days of mechanical ventilation. In the present study, we could perform no multivariate logistic regression analysis because of the few patients available.

Both the VV and venoarterial (VA) modes of ECMO have been used for the treatment of respiratory failure. VV access is generally the preferred mode of support for isolated respiratory failure, and it is often stated that VV ECMO should not be used in inotrope-dependent patients.[19] On the other hand, VA access is used when systemic arterial perfusion support is also necessary.[20] We selected VV ECMO for respiratory support in patients with severe respiratory failure but without heart failure. However, VA ECMO was selected if patients had severe respiratory failure with hypoxemia and respiratory acidosis resulting from hypercapnia that was refractory to conventional ventilation strategies. We would like to compare the effectiveness of VV and VA bypass in adult patients with severe respiratory failure.

In conclusion, the use of ECMO in adult patients is still controversial. However, our study showed fairly good results. It is assumed that the early introduction of ECMO is desirable if the causes of respiratory failure are recoverable. VV ECMO may be able to be removed if the weaning of ECMO flow can be started within 48 hours after ECMO introduction in patients with severe respiratory failure. On the other hand, it is believed that VV ECMO removal will be difficult if the ECMO flow cannot be weaned by 48 hr after ECMO introduction.

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