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Prognostic Predictors in Extracorporeal Membrane Oxygenation Treatment

Wen-Je Ko, MD, Yih-Sharng Chen, MD, Robert J. Chen, MD, MPH, Ching-Yuang Lin, MD*

From the Department of Surgery, National Taiwan University Hospital; and the Department of Pediatrics, Taipei Veteran General Hospital*, Taipei, Taiwan

Running title: prognostic predictors in ECMO treatment

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Address for reprints: Ching-Yuan Lin, MD, Department of Pediatrics, Taipei Veteran General Hospital, Taipei, Taiwan

Corresponding author: Wen-Je Ko, MD, Department of Surgery, National Taiwan University Hospital, 7 Chung-Shan S. Road, Taipei, Taiwan 100

Tel: 886-2-23123456 ext 3098

FAX: 886-2-23958747 E-mail: wenje@ha.mc.ntu.edu.tw

Abstract

Objective: The outcome of extracorporeal membrane oxygenation (ECMO) treatment is always unpredictable when it is not indicated for neonatal respiratory diseases. A prospective study was conducted to collect clinical, biochemical, immunological parameters at variable times during an ECMO course to determine which factors influenced ECMO outcome.

Methods: The patients' demography, pre-ECMO conditions, biochemistry, hematology, and arterial blood gas analysis during ECMO treatment, were recorded along with the duration, outcome and complications of the treatment. Blood was collected on the 3rd and 6th days after initiation of ECMO for cytokines study.

Results: Fifty patients who were receiving ECMO for acute cardio/pulmonary failure were studied; 32 were male, and 18 were female. Their ages ranged from 20 days to 84 years; their body weights ranged from 2.4 kg to 95 kg. ECMO was set up in operation rooms (n=20), intensive care units (n=18), cardiac catheterization rooms (n=3), emergency rooms (n=3), and outside hospitals (n=6). The indications of ECMO treatment included postcardiotomy cardiogenic shock (n=27), acute myocarditis (n=5), myocardial infarction that required resuscitation (n=7), cardiomyopathy with cardiogenic shock (n=2), acute respiratory distress syndrome (n=5), and others (n=4). Eleven patients died within 48 hours following initiation of

ECMO. The etiologies of mortality included extremely poor heart function (n=5), severe shock damage (n=5), and uncontrollable bleeding (n=1). Three patients died of brain death due to ECMO mechanical failure (n=1) or intracranial hemorrhage while on the ECMO (n=2). Sixteen patients underwent a successful ECMO treatment, but three of them died suddenly months later. Only 2 of 16 successful ECMO patients needed ECMO support for more than five days. The ECMO treatment of 20 patients failed and the patients died of multiple organs failure whether or not they were weaned off ECMO. Comparing instances of successful ECMO with those of failed ECMO by multiple logistic regression, revealed that three independent factors, acute renal failure at the time of ECMO set-up, sepsis during ECMO, lower IL-12 serum level on the 3rd day, predicted a failed ECMO treatment.

Conclusion: ECMO is an ideal rescue treatment for acute cardio/pulmonary failure, but a successful ECMO treatment requires the following: 1. Acute cardiopulmonary failure treated by ECMO must be rapidly reversible. ECMO is not intended for prolonged treatment. 2. No severe shock damage must have occurred due to underlying diseases before ECMO support is begun. 3. No complications can occur during ECMO.

Key word: extracorporeal membrane oxygenation, prognosis, acute renal failure, sepsis, cytokines, interleukin-12.

Word count: 386

Ultramini-abstract

Extracorporeal membrane oxygenation (ECMO) provides an ideal rescue treatment for acute cardio/pulmonary failure in critical patients. However, extremely poor heart function, very severe shock damage, and uncontrollable bleeding are contraindications of ECMO treatment. In those patients expected to benefit from ECMO treatment, acute renal failure at the time of ECMO set-up, sepsis during ECMO, and lower IL-12 serum level on the 3rd day predict the failure of ECMO treatment.

Although extracorporeal membrane oxygenation (ECMO) treatment has been primarily used for neonatal respiratory disease, [1] the number of patients undergoing such treatment has recently decreased because of new developments in surfactant therapy, NO inhalation, high frequency oscillatory ventilation, etc. [2] However, ECMO has become an ideal rescue treatment for acute cardiopulmonary failure in critical patients due to newly designed ECMO, including an improved vascular cannula, centrifugal pumps, microporous membrane oxygenators, heparin bound Carmeda bioactive surface and other developments. In fact, the use of ECMO in patients with circulatory collapse is increasing. [1]

Under current constraints on increasing medical costs, the cost of any expensive treatment must be justified. However, the outcome of ECMO treatment is always unpredictable especially when it is applied to critical patients. This prospective study evaluates the outcome of ECMO treatment of acute cardiopulmonary failure with different etiologies and collects clinical, biochemical, and immunological parameters at various times during ECMO treatment to determine which factors influenced ECMO outcome. More thoroughly understanding prognostic predictors of ECMO treatment can improve the success rate of ECMO treatment and make ECMO treatment more cost-effective.

Patients and methods

All patients who received ECMO support at the surgical department of National Taiwan University Hospital from October 2000 to September 2001 were prospectively enrolled in this study. ECMO has been employed for different extended indications in this hospital, including temporary support of non-heart-beating donors, [3] rescuing patient from acute massive pulmonary embolism, [4] replacing a cardiopulmonary bypass required in some operations of lung transplantations [5] and giant intracranial aneurysm [6]. After these extended ECMO indications had been excluded, 50 patients were included in this study.

The ECMO used was CB2505 (for patients with body weight $\geqq$12 kg) or CB2503 (for pediatric patients with body weight < 12kg), both from Medtronic Inc., Anaheim, CA, USA. The ECMO was composed of a centrifugal pump, and a microporous membrane oxygenator with an integrated heater. The entire ECMO system, including cannula, had a heparin bound Carmeda bioactive surface. A reflectance photometer (MX-2, Medtronic Inc., Anaheim, CA) was attached to the pre- and post-oxygenator circuit to monitor continuously blood oxygen saturation and hematocrit. ECMO priming, the cannulation technique, anticoagulation protocol, intensive care protocol, and ECMO weaning are described elsewhere. [7]

Recorded variables included age of the patients, sex, body weight, indication of

ECMO, pre-ECMO inotrope equivalent (IE, see note in Table 2), pre-ECMO blood lactate level, CPR before/during ECMO set-up, location of and route through which ECMO was established, ECMO duration, sepsis before ECMO set-up, sepsis during ECMO or within one week after the patient was weaned off ECMO (definition of sepsis: positive microorganism culture present in theoretically sterile area, for example, blood, pericardial cavity, pleural cavity; fever >38.5℃, blood WBC count > 15,000/mm^3 with shift to left in the differential count; clinical diagnosis of pneumonia or severe wound infection), acute renal failure requiring dialysis at ECMO set-up or later in the course, and the outcome and any complications of ECMO treatment. Arterial blood gas, hematology, serum biochemistry, including CK, CK-MB, AST, Bil, lactate, BUN, and Cr, were checked at least daily during ECMO treatment. Our previous study showed that ECMO survival patients could usually be weaned off ECMO after 4 to 6 days of ECMO support. [7] This study aimed to find which immunological factors on the 3rd day following initiation of ECMO predicted successful ECMO treatment, and which immunological factors on the 6th day were associated with ECMO treatment failure. Ten mL of blood were taken on the 3rd and 6th days to measure both the serum levels of proinflammatory cytokines, including IL-6, IL-8, IL-12, IL-17, IL-18, TNF-α, INF-γ, RANTES, MCP-1, and the total serum level of NO_2^{-1} and NO_3^{-1}, which measured iNOS activity.

IL-18 was measured by Sandwich ELISA test (Hayashibara Biochemical Labs., Inc) and IL-6, IL-8, IL-12, IL-17, RANTES, MCP-1, TNF- α , INF- γ were measured by Sandwich ELISA test (R & D System Inc, MN, USA). The concentrations of the total serum nitrite and nitrate were measured by colorimetric method (OXIS International Inc, OR, USA) to reveal nitride oxide production. This study was reviewed and funded by the Taiwan National Science Council.

Statistical analysis:

Numerical variables were tested by the Mann-Whitney U test, and categorical variables were tested by Fisher's exact test. Results at $P<0.05$ were considered significant.

Results

ECMO treatment for different diseases:

Thirty-two (64%) patients were male, and 18 were female. Their ages ranged from 20 days to 83.9 years with a median of 21.6 years. Their body weights ranged from 2.4 kg to 95.0 kg with a median of 50.0 kg. ECMO was set up in operation rooms for 20 patients, in intensive care units for 18, in cardiac catherization rooms for 3, in emergency service rooms for 3, and in outside hospitals for 6.

For those 6 patients at outside hospitals, we sent a team to the outside hospitals and set up ECMO there, and then transferred the patients under ECMO support to our hospital. Fifteen patients (30%) underwent ECMO for extracorporeal cardiopulmonary resuscitation (ECPR) while cardiac massage and epinephrine injection were being performed. Six of these 15 patients were weaned off ECMO and one was bridged to a centrifugal pump left ventricular assist device (VAD), but only 3 patients survived to discharge from hospital. After ECPR, brain death was noted in 3 patients; and a mild neurological defect was noted in 1 patient who, however, recovered later. Two ARDS patients received only VV-ECMO. Two ARDS patients received VA-ECMO initially, and were then shifted to VV-ECMO after the hemodynamics became stable. All other 46 patients in this study received only VA-ECMO.

Table 2 shows indications and outcomes of ECMO treatment. Postcardiotomy cardiogenic shock (PCS) was the most common indication of ECMO support. Two cases of PCS also involved respiratory failure, and ECMO was used to support both heart and lung. Fourteen patients required ECMO for PCS following operations for congenital heart defects, 8 of them could be weaned off ECMO but only 2 survived to hospital discharge. Six patients weaned off ECMO but died in the hospital due to sepsis (n=2), intracranial hemorrhage complicated by brain death (n=1), and sudden death (n=3, 39, 79, 115 days after ECMO wean-off).

Five patients received ECMO for acute myocarditis. One of them had mycoplasma myocarditis and encephalitis, and the other 4 patients had viral myocarditis. Brain death was noted in two patients following ECPR by ECMO, and in one patient following CPR due to ECMO mechanical failure. One patient was successfully weaned off ECMO but died of acute cholecystitis and uncontrolled sepsis 28 days after ECMO was removed.

Seven patients suffered acute myocardial infarction complicated with cardiogenic shock, and all of them received ECMO for ECPR. Two of them received percutaneous transcoronary angioplasty under ECMO support. One was weaned off ECMO but none survived to hospital discharge. Five received an emergent coronary artery bypass grafting under ECMO support. Three were weaned off ECMO and survived to hospital discharge.

Two patients received ECMO for circulatory collapse due to dilated cardiomyopathy. One was bridged to HeartMate left VAD and finally underwent heart transplantation. The patient remains alive 6 months after the transplantation. The

other patient required ECMO for ECPR, and hypoxic encephalopathy and acute renal failure were found after resuscitation. Although the patient was bridged to a centrifugal pump left VAD, he later died of multiple organ failure (MOF).

Five patients underwent ECMO for acute respiratory failure. The only case of survival was a kyphoscoliosis patient with pneumonia alone. Four other patients who died, had systemic diseases other than pneumonia alone. A patient with Wegener's granulomatosis suffered acute renal failure and lung hemorrhage complicated with pneumonia. A liver transplant recipient had pneumonia soon after transplantation. Two patients had pneumococcal pneumonia with septic shock.

Four patients received ECMO for various indications. The indications included a pulmonary hypertension crisis in a liver transplant recipient who had undergone an elective operation for chronic parasinusitis, acute occlusion of a modified Blalock-Taussig shunt in a patient with Tetralogy of Fallot; circulatory collapse due to choking, and lung hemorrhage as an operative complication in a patient with a large chest wall tumor.

Outcome of ECMO treatment:

Eleven patients (22%) died on ECMO support within 48 hours following initiation of ECMO. Five patients presented extremely poor cardiac function. The combined cardiac output of patients' native hearts and ECMO were not enough to support patients, and the patients died of circulatory

insufficiency. Five patients suffered brain death, anuria or oliguria, disseminated intravascular coagulation, and other problems, due to CPR before/during ECMO set-up, and soon died of severe shock damage. One patient died of uncontrollable lung hemorrhage due to an operative complication. This study noted brain death in at least 10 patients. Etiologies of brain death included ECPR (n=3), ECMO mechanical failure (n=1), intracranial hemorrhage (n=2), and pre-ECMO CPR (n=4).

Thirty-nine patients survived ≧ 3 days following initiation of ECMO support. A case of acute myocarditis had a complication of ECMO mechanical failure. Brain death was noted after the event, and might have been caused by a thromboembolism from the circuits or CPR itself during emergent ECMO change. Two patients suffered intracranial hemorrhage and brain death while on the ECMO support for PCS. One was a one-month-old, 2.5 kg male infant, and the other was a three-month-old, 4.1 kg female infant. ECMO was terminated and the patients died. These three patients died of direct complication of ECMO treatment, and they were therefore not included in the biochemistry and cytokine study.

Thirteen patients were weaned off ECMO support and survived to hospital discharge. Another three patients were weaned off ECMO and presented no evidence of MOF at the time of ECMO removal. However, the patients showed symptoms of congestive heart failure, and sudden cardiac death occurred 39, 79,and 115 days after ECMO removal. Mortality was unrelated to the ECMO event, and so ECMO treatment was successful in these 3 patients. The above 16 patients were considered to be “successful ECMO patients”. Only 2 of 16 successful ECMO patients required

ECMO support for more than 5 days. One was a heart transplant recipient, who had primary graft dysfunction manifest in the right heart failure and required ECMO support for 221 hours. The other patient was a case of ARDS, and required ECMO for 594 hours.

Nine patients were weaned off ECMO support but showed evidence of MOF at the time of ECMO removal. They died of MOF 17±14 days following removal of ECMO. Eleven patients could be not weaned from ECMO and died of MOF while on ECMO support. These 20 patients were considered to be “failed ECMO patients”. We compared demography, pre-ECMO condition, biochemistry and some clinical data between the successful ECMO patients and failed ECMO patients in Table 2.

Prognostic predictors of ECMO outcome:

An attempt was made to identify the indicators of shock damage that predicted the outcome of ECMO treatment. However, pre-ECMO IE, pre-ECMO blood lactate levels, CPR, peak CK, CK-MB, and AST levels in the first 3 days, and peak Bil, maximum WBC count, minimum platelet count in the first week, were not different between the successful ECMO patients and failed ECMO patients. Only the variable “acute renal failure at the time of ECMO set-up” showed a significant difference between the two groups, and is a good indicator of shock damage to predict late MOF

and mortality. Variables CK, CK-MB, blood lactate levels on the 3rd day, and CK, CK-MB, AST levels on the 6th day, differed between the two groups. These variables indicated persistent damage during ECMO treatment and higher values were associated with ECMO treatment failure.

Figure 1 shows that the failed ECMO patients had significantly higher serum levels of IL-18, IL-17, IL-6, IL-8, MCP-1 on the 3rd day, and significantly higher serum levels of IL-17, Il-6, IL-8, TNF- α on the 6th day than their successful ECMO counterparts. Persistent elevation of proinflammatory cytokines levels, including IL-18, IL-17, IL-6, IL-8, TNF- α , and MCP-1, contributed to MOF and subsequent mortality. Notably, the failed ECMO patients had significantly lower IL-12 serum levels on the 3rd day than the successful ECMO patients, but higher IL-12 serum level on the 6th day. This “early-low, late-high” pattern in the IL-12 blood level was associated with mortality in ECMO patients. To build a model to predict ECMO outcome, we combined all variables in Table 2 and Figure 1 to perform a logistic regression analysis. Significant predictors ($p<0.2$) from simple logistic regression analyses were selected. With colinearity eliminated, multiple logistic regression was conducted by backward stepwise selection method. The significant predictors in the final model were acute renal failure at the time of ECMO set-up (odds ratio=28, 95% confidence interval: 4.43~176.8, $p<0.001$), sepsis from ECMO set-up to one week

following ECMO removal (odds ratio=5.30, 1.14~24.54, p=0.033), and IL-12 serum level on the 3rd day (odds ratio=0.95, 0.896~0.999, p=0.049). These results imply that the presence of acute renal failure at ECMO set-up, sepsis during ECMO, and lower IL-12 serum levels on the 3rd day were positive predictors of failed ECMO treatment.

Discussion

Advantages of use of ECMO in critical patients:

ECMO could be applied in different patients with very different ages and body weights. Other forms of mechanical circulatory support like the intra-aortic balloon pump and VAD have limited use in smaller patients. ECMO has two modes. VV-ECMO can replace only lung function. VV-ECMO is enough, if a patient has respiratory failure but has good heart function. VA-ECMO can support both heart and lungs. ECMO support could be applied for acute cardiopulmonary failure due to diverse etiologies. In comparison, VAD can provide only circulatory support. The ECMO design that included a microporous membrane oxygenator and a centrifugal pump enabled rapid priming. Less than 30 min was required to establish the ECMO support in our hospital. Cannulation of peripheral vessels enabled ECMO to be used as a bedside procedure under local anesthesia. In our hospital, all instruments and ECMO parts required for ECMO set-up are packed and put on a cart. When ECMO support was required, a team was sent to the site with the ECMO cart and ECMO was set up there. We could provide emergent ECMO support to patients in operation rooms, intensive care units, cardiac catheterization rooms, emergence service rooms, and even in other hospitals. After ECMO had been set-up, the patient was transported to a special ICU for further care. All these advantages made ECMO an ideal rescue treatment for cardiopulmonary failure in critical patients, and ECPR was made possible by ECMO.

ECMO can stabilize critical patients, and thus allow a physician reasonable time to decide the next step, which may involve waiting for recovery, heart/lung transplantation, coronary artery bypass grafting, bridging to more permanent devices like VAD, or giving-up. This study noted brain death in at least 10 patients, and more patients were noted to have suffered severe shock damage that made long-term survival impossible. Further aggressive treatment was omitted in these patients. ECMO can prevent misuse of more expensive treatment modalities like VAD in

unpredictably critical patients.

Limitation of ECMO treatment:

ECMO is not intended for long-term support. Only 2 survival patients in this study required ECMO support for more than 5 days; one was an ARDS patient, and the other was a heart transplant recipient. As expected, recovery of the ARDS needed a longer time. Primary graft dysfunction with the right heart failure has been reported to need longer ECMO support than ordinary PCS. [8] For other patients, either heart function recovered, or complications supervened and prevented recovery. Therefore, a definite treatment plan should be decided early during ECMO.

Eleven patients (22%) died under 48 hours after ECMO support was initiated. Smedira reported a similar 24% 3-day mortality rate in adult patients who received ECMO support for heart failure. [9] ECMO can provide only partial circulatory support, and the combined output of a patient's native heart and ECMO must suffice to support that patient. Our previous report showed that ECMO provided 2.53±0.84 L/min blood flow in adult patients. [7] This amount flow is not enough for an adult patient with a motionless heart. The patient's heart must contribute some required cardiac output. ECMO alone cannot provide full circulatory support, especially in adult patients. Several patients in this study had sustained severe shock damage before initiation of

ECMO support. The complications of severe shock damage such as brain death precluded survival. Although these complications could not be foreseen before ECMO, their existence led to a poor prognosis and should preclude further aggressive treatment. ECMO itself, of course, cannot treat uncontrollable bleeding. In a word, extremely poor heart function, very severe shock damage, and uncontrollable bleeding are contraindications of ECMO support. Patients with these problems were not good candidates for ECMO support, because they did not benefit from ECMO treatment. In fact, a most important complication of ECMO was its abuse or misuse.

Factors that influence ECMO outcome:

In this study, 3 children were successfully weaned off ECMO, but months later died suddenly. The children presented no evidence of other organ damage except persistent heart failure post-ECMO. The same finding has been reported in adult patients who received ECMO support for PCS. [7] Persistent heart failure predicts risk of sudden death in ECMO-weaned patients. For these patients, arrhythmia prophylaxis is necessary or early heart transplantation is indicated.

Monocyte/macrophage-derived cytokines such as IL-6, IL-8 and TNF-α appear to play a pivotal role in local immunological activation, leading to tissue destruction. [10-12] IL-17, secreted only by $CD4^+$-activated memory T cells, directly activates

endothelial cells to generate IL-6, IL-8, MCP-1, PGE_2, NO and granulocyte-CSF. [13] Additionally, IL-17 sustains the maturation CD34-hematopoietic progenitors into neutrophils, [11, 12, 14] suggesting that IL-17 plays some role in innate response. [14] IL-18 is a member of the IL-1 cytokine family, and it is produced by macrophages, Kupffer cells, keratinocytes, fibroblasts, chondrocytes, and osteoblasts. IL-18 directly induces both IFN-γ production by NK cells and NK cytotoxicity. [15] IL-18 induces cytokine and chemokine release from neutrophils; upregulates CD11b expression; induces granule release; and enhances the respiratory burst following exposure to fMLP. [15] Consequently, IL-18 promotes an innate immune response and a Th1 response. [16] These data indicate that IL-18 is important in developing and sustaining inflammatory pathogenic states. This study found that high levels of serum proinflammatory cytokines including IL-18, IL-17, IL-6, IL-8 and MCP-1 on the 3rd day increasing to the 6th day might be associated with a poor prognosis. This indicates that over-activation of innate immunity may lead to a fatal outcome. IL-12, defined as Th1 cytokines, contributes to inflammation. In an experiment with baboons given an *E. coli* injection, a lower peak level of IL-12 was noted in the baboons that received a lethal *E. coli* injection than in the baboons that were injected with sublethal amount. This finding sharply contrasted with higher levels of other cytokines, such as TNF-α, IL-6, and IL-8. [17] Similar results were noted in our study, an initially low level of

IL-12 on the 3rd day and a high level of IL-12 on the 6th day were associated with a fatal outcome of ECMO treatment.

Clinical data, biochemistry tests, and serum cytokines were analyzed in these patients who were expected to benefit from ECMO. Three independent factors were found to predict failure of ECMO treatment. These 3 factors were acute renal failure at the time of ECMO set-up, sepsis during ECMO, and lower IL-12 blood level on the 3rd day following initiation of ECMO. Acute renal failure at ECMO set-up implies that severe shock damage had occurred before ECMO treatment was begun and this factor was a good indictor of shock damage to predict a failed ECMO outcome. Sepsis during ECMO course increased the risk of MOF and thereby reduced the likelihood of survival. Without ECMO, the patients would have died before the 6th day, and the increased level of IL-12 on the 6th day might represent a desperate response to impending death. Therefore, Il-12 blood levels on the 3rd day were more clinically meaningful. ECMO mortality patients had lower IL-12 but higher levels of other proinflammatory cytokines on the 3rd day than did their surviving counterparts. In short, shock damage, sepsis, and immunological dysregulation reduced the likelihood of successful ECMO treatment in patients with acute cardiopulmonary failure.

Conclusion:

Successful ECMO treatment requires the following: 1. Acute cardiopulmonary failure treated by ECMO must be soon reversible. ECMO is not intended for prolonged treatment, and it serves only as a temporary partial cardiopulmonary support until recovery or bridging to other more permanent treatment. 2. No severe shock damage due to the underlying diseases can have occurred before ECMO support is initiated. 3. No complications such as mechanical failure, sepsis, or others, can have occurred during ECMO treatment. An initially low level of IL-12 on the 3rd day, rebounding to a high level on the 6th day, accompanied with a high level of serum proinflammatory cytokines including IL-18, IL-17, IL-6, IL-8 and MCP-1 on the 3rd day increasing to the 6th day may be associated with a poor prognosis. Therefore, improving the success rate of ECMO treatment requires the following: 1. Good case selection. 2. Sufficiently early initiation of ECMO support. 3. Intensive ECMO care and monitoring of prognostic factors.

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References

1. ECLS registry report. international summary. *Extracorporeal Life Support Organization* 2002 Jan.

2. Hintz SR, Suttner DM, Sheehan AM, Rhine WD, Van Meurs KP. Decreased use of neonatal extracorporeal membrane oxygenation (ECMO): how new treatment modalities have affected ECMO utilization. *Pediatrics* 2000;106:1339-43.

3. Ko WJ, Chen YS, Tsai PR, Lee PH. Extracorporeal membrane oxygenation support of donor abdominal organs in non-heart-beating donors. *Clin Transplant* 2000;14:152-6.

4. Hsieh PC, Wang SS, Ko WJ, Han YY, Chu SH. Successful resuscitation of acute massive pulmonary embolism with extracorporeal membrane oxygenation and open embolectomy. *Ann Thorac Surg* 2001;72:266-7.

5. Ko WJ, Chen YS, Lee YC. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. *Artif Organs* 2001;25:607-12.

6. Chen YS, Ko WJ, Lin FY, Huang SC, Wang SS, Tu YK. New application of heparin-bounded extracorporeal membrane oxygenation in difficult neurosurgery. *Artif Organs* 2001;25:627-32.

7. Ko WJ, Lin CY, Chen RJ, Wang SS, Lin FY, Chen YS. Extracorporeal

membrane oxygenation support for adult post-cardiotomy cardiogenic shock. *Ann Thorac Surg* 2002;73:538-45.

8. Fiser SM, Tribble CG, Kaza AK, Long SM, Zacour RK, Kern JA, et al. When to discontinue extracorporeal membrane oxygenation for postcardiotomy support. *Ann Thorac Surg* 2001;71:210-4.

9. Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone HE, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: Survival at five years. *J Thorac Cardiovasc Surg* 2001;122:92-102.

10. Hsieh HG, Loong CC, Lui WY, Chen A, Lin CY. IL-17 expression as a possible predictive paramedter for subclinical renal allograft rejection. *Transpl Int* 2001;14:287-98.

11. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, et al. T-cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J Exp Med* 1996;183:2593-603.

12. Albanesi C, Cavani A, Girolomoni G. IL-17 is produced by nickel-specific T lymphocytes and regulates ICAM-1 expression and chemokine production in human keratinocytes:synergistic or antagonist effects with IFN-γ and TNF-α. *J Immunol* 1999;162:494-502.

13. Antonysamy MA, Fanslow WC, Fu F, Li W, Qian S, Troutt AB, et al. Evidence for a role of IL-17 in organ allograft rejection: IL-17 promotes the functional differentiation of dendritic cell prognitors. *J Immunol* 1999;162:577-84.

14. Witowski J, Pawlaczyk K, Breborowicz A, Scheuren A, Kuzlan-Pawlaczyk M, Wisniewska J, et al. IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GROα chemokine from mesothelial cells. *J Immunol* 2000;165:5814-21.

15. Leung BP, Culshaw S, Gracie JA, Hunter D, Canetti CA, Campbell C, et al. A role for IL-18 in neutrophil activation. *J Immunol* 2001;167:2879-86.

16. Xu D, Trajkovic V, Hunter D, Leung BP, Schulz K, Gracie JA, et al. IL-18 induces the differentiation of Th1 or Th2 cells depending upon cytokine milieu and genetic background. *J Immunol* 2000;30:3147-56.

17. Jansen PM, van der Pouw Kraan TC, de Jong IW, van Mierlo G, Wijdenes J, Chang AA, et al. Release of interleukin-12 in experimental Escherichia coli septic shock in baboons: relation to plasma levels of interleukin-10 and interferon-gamma. *Blood* 1996;87:5144-51.

Figure Legend

Figure 1. Comparison of plasma cytokines levels between successful ECMO patients and failed ECMO patients on the 3rd and 6th days following initiation of ECMO treatment. Bars represent ± standard error around the mean.

*: $p<0.05$, **: $p<0.01$ by Mann-Whitney U test.

Table 1: indication and outcome of ECMO treatment

		Sex	Age (yr)	Outcome	
Indication	n	(M/F)	Range, median	Wean-off	Discharge alive
PCS	27	17/10	0.1~73.5, 2.1	15 (56%)	7 (26%)
CHD (n=14)		6/8	0.1~14.7, 0.2	8 (57%)	2 (14%)
CAD (n=9)		7/2	6.8~73.5, 57.2	4 (44%)	3 (33%)
HTx (n=3)		3/0	2.5~60.8, 5.8	2 (66%)	1 (33%)
VHD (n=1)		1/0	46.7	1 (100%)	1 (100%)
Acute myocarditis	5	2/3	9.8~65.0, 20.1	3 (60%)	1 (20%)
AMI & ECPR	7	7/0	40.6~67.8, 58.8	4 (57%)	3 (43%)
DCM	2	2/0	18~ 58,	--	1 (50%)
ARDS	5	2/3	2.9~61.8, 20.6	1 (20%)	1 (20%)
other	4	2/2	1.8~83.9, 36.5	1 (25%)	0 (0%)

AMI: acute myocardial infarction, ARDS: acute respiratory distress syndrome, CAD: coronary artery disease, CHD: congenital heart disease, DCM: dilated cardiomyopathy, ECMO: extracorporeal membrane oxygenation, ECPR: extracororeal cardiopulmonary resuscitation, HTx: heart transplantation, PCS: post-cardiotomy cardiogenic shock, VHD: valvular heart disease

Table 2 Comparison between successful ECMO patients and failed ECMO patients

	Successful ECMO (n=16)	Failed ECMO (n=20)	P
Sex (M/F)	12/4	13/7	0.517
Age (yr)	31.6 ±27.3	28.1 ±28.7	0.787
Body weight (kg)	43.7 ±32.2	41.7 ±31.4	0.975
ECMO duration (hr)	116.6 ±135.7	188.9 ±133.5	0.011*
Pre-ECMO condition:			
I.E.	30.3 ±15.0	38.4 ±32.9	0.942
Blood lactate (m mole/L)	10.6 ±5.8	11.9 ±6.2	0.512
CPR (+/-)	6/10	13/7	0.101
ARF at ECMO set-up (+/-)	2/14	16/4	0.000*
Sepsis at ECMO set-up (+/-)	1/15	5/15	0.134
Sepsis during/after ECMO (+/-)	3/13	11/9	0.027*
Peak CK (U/L)	2661 ±2090	26229 ±41483	0.114
Peak AST (U/L)	542 ±828	1731 ±2790	0.279
Peak Bil (mg/dL)	3.7 ±3.0	6.8 ±6.5	0.272
Max WBC count ($x10^3/mm^3$)	15.6 ±6.2	21.3 ±1.1	0.111
Min platelet count ($x10^3/mm^3$)	30.9 ±15.5	23.2 ±13.8	0.107
3^{rd} day after ECMO initiation:			
CK (U/L)	1980 ±2090	26852 ±41701	0.031*

CK-MB (U/L)	65.4 ±73.6	626.0 ±1130.3	0.010*
AST (U/L)	158 ±131	1140 ±2088	0.280
Bil (mg/dL)	2.4 ±1.6	4.7 ±4.2	0.144
Blood lactate (mmole/L)	2.6 ±1.8	5.5 ±4.5	0.011*
Platelet count ($x10^3/mm^3$)	50.5 ±37.3	48.3 ±25.0	0.726
PaO_2/FiO_2	233 ±133	306 ±180	0.226
6^{th} day after ECMO initiation:			
CK (U/L)	942 ±940	12394 ±20146	0.049*
CK-MB (U/L)	23.6 ±12.9	238.7 ±273.4	0.000*
AST (U/L)	160 ±237	394 ±456	0.049*
Bil (mg/dL)	3.6 ±2.6	8.4 ±7.2	0.121
Blood lactate (mmole/L)	2.0 ±1.2	3.4 ±2.7	0.198
Platelet count ($x10^3/mm^3$)	60.3 ±22.6	46.2 ±30.6	0.104
PaO_2/FiO_2	243 ±149	240 ±200	0.275

ARF: acute renal failure (requiring dialysis), AST: aspartate aminotransferase, Bil: bilrubin, CK: creatinie kinase, CK-MB: creatine kinase MB fraction, CPR: cardiopulmonary resuscitation, ECMO: extracorporeal membrane oxygenation, IE: inotrope equivalent (dosages of dopamine + dobutamine (in mcg/kg/min) + (dosages of epinephrine + norepinephrine + isoproterenol (in mcg/kg/min)) x 100 + dosages of milrinone (in

mcg/kg/min) x 15)

Peak CK, Peak AST: the highest value in the first 3 days after initiation of ECMO treatment

Peak Bil, Max WBC, Min Platelet: the highest and lowest value in the first week after initiation of ECMO treatment

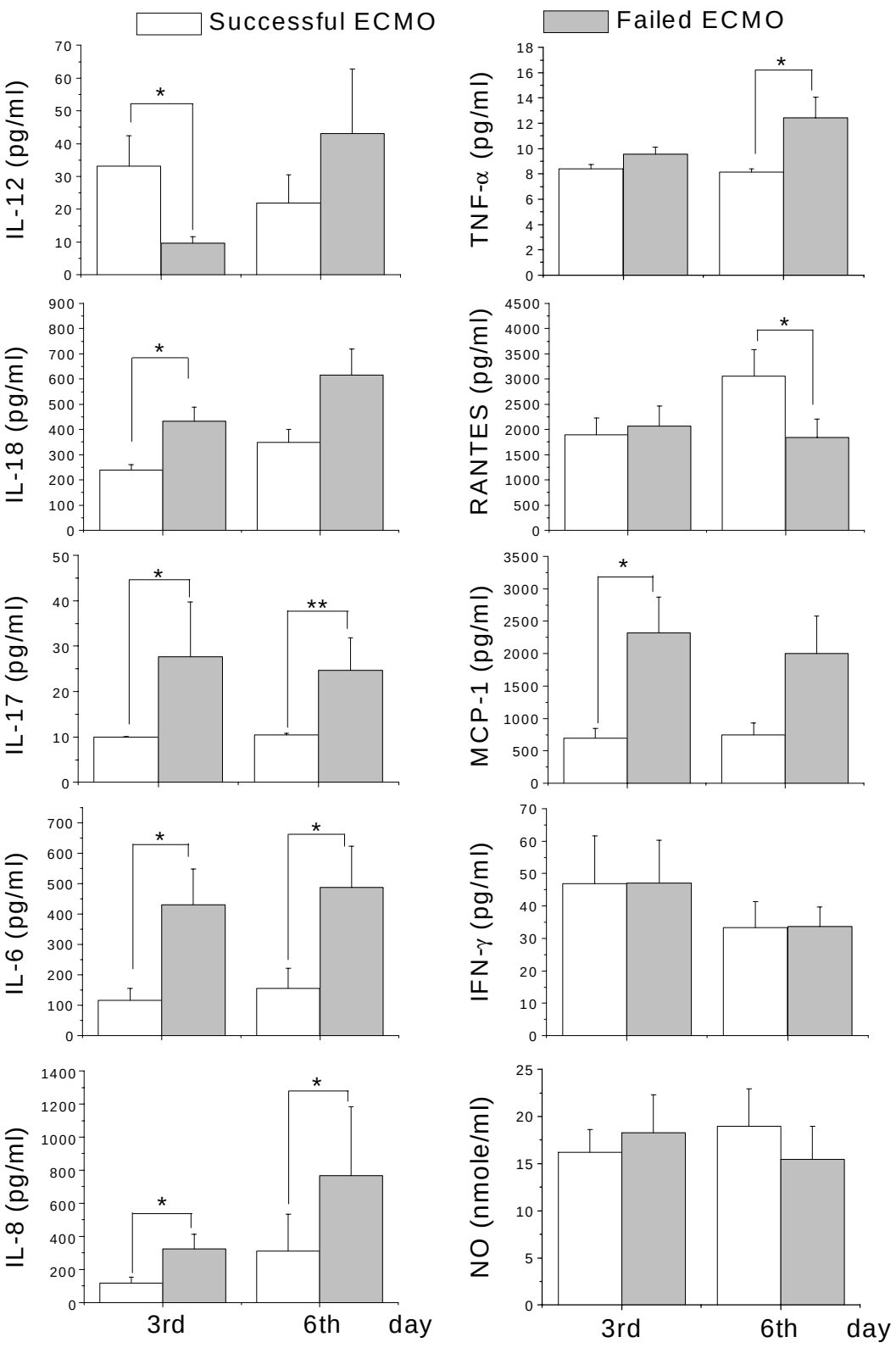
Successful ECMO
Failed ECMO
IL-12 (pg/ml)
TNF-α (pg/ml)
IL-18 (pg/ml)
RANTES (pg/ml)
IL-17 (pg/ml)
MCP-1 (pg/ml)
IL-6 (pg/ml)
IFN-γ (pg/ml)
IL-8 (pg/ml)
NO (nmole/ml)
3rd
6th
day

fig 1.