Extracorporeal membrane oxygenation for refractory septic shock in adults

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Abstract

OBJECTIVES: The role of extracorporeal membrane oxygenation (ECMO) remains controversial in adult patients with refractory septic shock. We sought to describe the clinical outcomes of adult patients supported by ECMO during septic shock refractory to conventional treatment.

METHODS: We analysed consecutive adult patients with refractory septic shock, assisted by an ECMO system between January 2005 and December 2013 in a single-centre registry. The primary outcome was survival to hospital discharge.

RESULTS: A total of 32 patients (21 males) received ECMO support for refractory septic shock. Of these, 14 patients (43.8%) had undergone cardiopulmonary resuscitation (CPR) and 7 patients (21.9%) did not achieve the return of spontaneous circulation until initiation of ECMO flow. ECMO was weaned off successfully in 13 patients (40.6%) and 7 patients (21.9%) survived to hospital discharge. The survivors had lower peak lactate (4.5 vs 15.1 mmol/l, P = 0.03), lower Sepsis-related Organ Failure Assessment day 3 score (15 vs 18, P = 0.01) and higher peak troponin I (32.8 vs 3.7 ng/ml, P = 0.02) than the non-survivors. None of the patients (31.3%) in whom ECMO was initiated more than 30.5 h after onset of septic shock, survived. In multivariable-adjusted models, CPR [adjusted hazard ratio (HR), 4.61; 95% confidence interval (CI), 1.55–13.69; P = 0.006] was an independent predictor of in-hospital mortality after ECMO in patients with refractory septic shock. Higher peak troponin I > 15 ng/ml (adjusted HR, 0.34; 95% CI, 0.12–0.97; P = 0.04) was associated with a lower risk of in-hospital mortality.

CONCLUSIONS: Survival to hospital discharge remained low in adult patients with refractory septic shock despite ECMO support. Our findings suggest that implantation of ECMO during refractory septic shock could be considered in patients with severe myocardial injury but should be avoided in patients who have received CPR.

Keywords: Septic shock • Extracorporeal membrane oxygenation • Cardiopulmonary resuscitation • Myocardial injury

INTRODUCTION

Septic shock is a common and serious disorder with high mortality [1, 2]. For septic shock unresponsive to all conventional treatments, extracorporeal membrane oxygenation (ECMO) becomes a salvage therapy to consider in neonates and children [3, 4]. The use of ECMO remains controversial in adults with refractory septic shock, although a few cases have reported successful outcomes with ECMO support [5–8]. Furthermore, a recently published study showed good long-term clinical outcomes and suggested that ECMO might be a valuable option in adult patients with refractory cardiac dysfunction during severe bacterial septic shock [9]. Therefore, we sought to investigate the clinical outcomes of adult patients supported by ECMO during refractory septic shock from an ECMO registry at our institution.

MATERIALS AND METHODS

Study population

We retrospectively reviewed our registry of patients who received ECMO support between January 2005 and December 2013. ECMO was indicated in patients with refractory shock, defined as evidence of organ hypoperfusion (extensive skin mottling, progressive lactic acidosis, oliguria or altered mental status) despite adequate intravascular volume and the inability to maintain mean arterial pressure >65 mmHg despite infusion of very high-dose catecholamines (norepinephrine > 1 μg/kg/min, dopamine > 20 μg/kg/min or epinephrine > 1 μg/kg/min with dobutamine > 20 μg/kg/min) [3, 10]. Patients were eligible for the study if they were 18 years of age or older; ECMO was implanted for sepsis, defined...
as clinical signs of infection and evidence of pathogenic microorganisms according to culture or serological tests. The Institutional Review Board of Samsung Medical Center approved this study and waived the requirement for written informed consent.

Extracorporeal membrane oxygenation implantation and management

The decision to implant ECMO for mechanical support was determined by an experienced team, and the ECMO was placed at bedside or in a fluoroscopy room by cardiovascular surgeons or interventional cardiologists. Capiox Emergency Bypass System (Capiox EBS™; Terumo, Inc., Tokyo, Japan) and Permanent Life Support (PLS; MAQUET, Germany) were used in our hospital. These systems are composed of a portable controller with a back-up battery, a disposable bypass circuit integrated with a heparin-coated membrane oxygenator and a centrifugal pump. Device insertion was performed by percutaneous cannulation using the Seldinger technique. Surgical cannulation using the cut-down method was performed in difficult cases. Cannula sizes ranged from 14 to 21 French for the femoral artery and from 21 to 28 French for the femoral vein. In the event of distal limb ischaemia after arterial cannulation, a catheter was inserted distal to the cannulation site for limb perfusion.

We previously reported detailed management [11] in which continuous unfractionated heparin was infused intravenously to maintain an activated clotting time between 180 and 220 s. The revolutions per minute of the ECMO device were initially set to achieve an ideal cardiac index >2.2 l/min/body surface area (m²) and were adjusted to target a central mixed venous saturation >70% and a mean arterial pressure >65 mmHg. Inotropes were discontinued or reduced to minimal doses within a few hours of achieving goal-directed flows. Echocardiography was performed daily to monitor cardiac function. If patients were haemodynamically stable and adequately oxygenated, they were considered for ECMO weaning when the flow rate was 1 l/min/m² for 4 h. Successful weaning was defined as disconnection of the patient from ECMO without reinsertion or death within 24 h.

Data collection and outcome variables

The primary outcome of the study was survival to hospital discharge. The following detailed data were obtained through medical record review: age, gender, comorbidities, infection site, microbiology results and laboratory data during the first 24 h of ECMO implantation. Echocardiography was performed, and left ventricular dimension and ejection fraction were recorded. Severity of illness was assessed by the Simplified Acute Physiology Score (SAPS) 3 [12]. Sepsis-related Organ Failure Assessment (SOFA) score [13] and number of failing organs. SAPS 3 was measured as the worst value during the first hour of admission to the intensive care unit (ICU). SOFA scores were recorded as the last value before initiation of ECMO and were monitored daily until transfer to the general ward. Failing organs were defined as those with a SOFA score of 2 or higher. Shock-to-ECMO interval was defined as the time from the initiation of vasoactive drugs to the start of ECMO flow. Appropriate antibiotic therapy was considered if at least one of the prescribed antibiotics on the day of the ECMO implantation had sensitivity against the identified pathogens, based on in vitro susceptibility testing. Other outcome variables included successful weaning from ECMO, duration of ECMO support, length of stay in the ICU, SOFA score on Day 3, peak lactate level and peak troponin I value. Safety outcomes included limb ischaemia requiring surgical or interventional therapy, gastrointestinal bleeding and stroke (identified by the occurrence of new neurological symptoms with evidence of ischaemia or haemorrhage on computed tomography).

Statistical analysis

All values are presented as numbers with percentages for categorical variables and median with interquartile range for continuous variables. Comparisons between continuous variables were made using a Wilcoxon rank-sum test, and categorical data were analysed using Fisher’s exact test. The receiver operating characteristic curve was used to evaluate the cut-off value and discrimination power of continuous variables for predicting survival outcome. The c-statistic is equivalent to the area under the receiver operating characteristic curve. Event-free survival curve was estimated by the Kaplan–Meier method and compared using the log-rank test. We used Cox proportional hazard regression models to identify potential prognostic factors. Proportional hazard assumptions were confirmed by Schoenfeld’s tests, and no relevant violation was found. Multivariable Cox proportional hazard regression models were fitted to determine factors that independently contributed to outcomes. To reduce overfitting, potential confounders were adjusted using a backward elimination method based on the Akaike information criterion [14]. We selected covariates that were clinically relevant and those with P-values < 0.2 on univariable analyses, including age, chronic kidney disease, SOFA score, cardiopulmonary resuscitation (CPR), peak troponin I > 15 ng/ml, renal replacement therapy and appropriate antibiotic therapy. We fitted a model further adjusted for CPR duration in order to determine independent factors in patients who underwent CPR. All tests were two-tailed, and P-value < 0.05 was considered statistically significant. All analyses were performed using the R software version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Among the 696 adult patients who underwent ECMO between January 2005 and December 2013, a total of 32 consecutive patients with refractory septic shock were enrolled in this study. The baseline characteristics are given in Table 1. The median age was 55 (interquartile range (IQR), 44–63) years, and 21 patients (65.6%) were immunocompromised. Underlying conditions of immunocompromised hosts were organ transplantation in 9 patients (liver in 5, kidney in 3, heart in 1), bone marrow transplantation in 2 patients, chemotherapy for malignancy in 5 patients (haematological malignancy in 4, solid tumour in 1) and steroid or cytotoxic drug therapy in 5 patients. Diabetes (53.1%) was the most common comorbid disease. Three patients had a history of ischaemic heart disease, but coronary angiography revealed no significant lesions. At ECMO implantation, 26 patients underwent echocardiography, and 22 patients (84.6%) had left ventricular dysfunction with ejection fraction <50%. The median SAPS 3 was 79 (IQR, 76–85) on ICU admission, the median SOFA score was 16 (IQR, 14–18) and the
number of failing organs at ECMO initiation was 3 (IQR, 2–3). The cannulae were placed successfully at the femoral vein and artery in all patients. Surgical cannulation was performed using the cut-down method in 2 patients: because of failure of percutaneous cannulation in 1 patient, and for presurgical pneumatosis intestinalis in the other patient. The median shock-to-ECMO interval was 23.5 (IQR, 10.3–33.5) h, and none of the patients (31.3%) in whom ECMO was initiated more than 30.5 h from onset of shock, survived (Fig. 1). Fourteen patients received CPR, and the median duration of CPR was 23.0 (IQR, 7.5–41.8) min. The initial rhythm at cardiac arrest was asystole or pulseless electrical activity in 12 patients (85.7%) and ventricular tachycardia or fibrillation in 2 patients (14.3%). Seven patients did not achieve the return of spontaneous circulation until initiation of ECMO flow. Information about the infected sites and micro-organisms are detailed in Table 2. The most frequently infected site was the lung, and 20 patients had bacteraemia. *Streptococcus species* and *Escherichia coli* were the most common Gram-positive and Gram-negative bacteria, respectively.

**Clinical outcomes**

Observed clinical outcomes are given in Table 3. Of 32 patients, 7 survived to hospital discharge. Nineteen patients died from refractory shock combined with multiple organ failure. Thirteen patients were successfully weaned from ECMO, but 6 patients eventually expired, secondary to sepsis in 4 patients, splenic vein rupture in 1 patient and massive brain haemorrhage in 1 patient. In addition to brain haemorrhage, 1 patient developed peptic ulcer bleeding and underwent endoscopic haemostasis. Limb ischaemia occurred in 5 patients. One patient suffered compartment syndrome and required foot amputation despite emergent revision of the cannula.

**Comparison of survivors and non-survivors**

At baseline, SOFA score, blood lactate and troponin I were similar between the non-survivor and survivor groups. However, the survivors had lower SOFA score at Day 3 (survivors vs non-survivors,
vs 18, \( P = 0.01 \) and lower peak lactate level (4.5 vs 15.1 mmol/l, \( P = 0.03 \)) compared with the non-survivors. As shown in Fig. 2, SOFA score at Day 3 and peak blood lactate had an increasing tendency compared with baseline values in non-survivors. Myocardial injury as evaluated by peak troponin I value was higher in survivors than in non-survivors (32.8 vs 3.7 ng/ml, \( P = 0.02 \)), and the best discriminative value of peak troponin I level for predicting survival to hospital discharge was determined to be 15 ng/ml (specificity = 0.75, sensitivity = 1.00, c-statistic = 0.84, Fig. 3). Only 2 patients survived after CPR, in whom the duration of CPR was 4 and 5 min, respectively (4.5 vs 26.0 min, \( P = 0.07 \)).

The survival analysis using the Kaplan–Meier method showed that patients who received CPR had a higher rate of all-cause death during the follow-up period than those who did not (log-rank, \( P = 0.009 \), Fig. 4).

**Predictor of in-hospital mortality**

Predictors of in-hospital mortality are presented in Table 4. In univariable analyses, baseline SOFA score and CPR were found to differ significantly between the survivors and the non-survivors. Higher peak troponin I showed a trend towards lower risk of in-hospital mortality, and longer CPR duration showed a trend...
towards higher risk of in-hospital mortality. In multivariable-adjusted models, CPR [adjusted hazard ratio (HR), 4.61; 95% confidence interval (CI), 1.55–13.69; P = 0.006] was an independent predictor of in-hospital mortality after ECMO in patients with refractory septic shock. Higher peak troponin I > 15 ng/ml (adjusted HR, 0.34; 95% CI, 0.12–0.97; P = 0.04) was associated with a lower risk of in-hospital mortality. In patients who underwent CPR, longer CPR duration and higher baseline SOFA score were associated with a higher risk of in-hospital mortality.

**DISCUSSION**

We performed this retrospective cohort study of adults who were supported by ECMO for refractory septic shock. The main findings of this study are as follows: (i) survival of adult patients with refractory septic shock was 22% (7/32) in spite of ECMO support; (ii) CPR was an independent predictor of in-hospital mortality after ECMO in patients with refractory septic shock. Higher peak troponin I > 15 ng/ml (adjusted HR, 0.34; 95% CI, 0.12–0.97; P = 0.04) was associated with a lower risk of in-hospital mortality. In patients who underwent CPR, longer CPR duration and higher baseline SOFA score were associated with a higher risk of in-hospital mortality.
initiation of ECMO. Only two of these patients survived, and they recovered spontaneous circulation within 5 min after cardiac arrest. The survival analysis using Kaplan-Meier method showed that patients receiving CPR had a higher rate of in-hospital mortality during the follow-up period than those who did not. In multivariable models adjusted by potential confounders, CPR was an independent predictor of in-hospital mortality. These findings suggest that the use of ECMO might be contraindicated in patients who developed cardiac arrest associated with refractory septic shock.

Second, our patients had less severe myocardial dysfunction compared with the patients in Brechot et al., as evidenced by a higher left ventricular ejection fraction [25% (20–41%) in this study vs 16% (10–30%) in Brechot et al.]. Most of the enrolled patients in another recently published study with unfavourable outcomes also paradoxically had preserved left ventricular function [18]. The paradoxical relationship between myocardial injury and better survival could be explained by the pathophysiology of refractory septic shock and the reversibility of septic cardiomyopathy. There are two haemodynamic patterns of early death in septic shock: distributive shock (low systemic vascular resistance and refractory hypotension despite preserved cardiac index) or a cardiogenic form of septic shock (decreased cardiac index) [19]. Distributive shock may be related to a maldistribution of blood flow at the organ level or microvascular level [20], and ECMO might be of little value in patients with distributive shock who present with lower normal or supranormal cardiac function. However, ECMO may support decreased cardiac output in patients with the cardiogenic form of septic shock that is unresponsive to very high doses of catecholamines [21]. Several studies have shown that myocardial dysfunction in septic cardiomyopathy is transient and reversible [22–24]. Infection is also a reversible factor if the source of infection is controlled by appropriate antibiotics or drainage intervention. Consequently, ECMO could provide extra time for recovery of the failing heart and support the perfusion of major organs until cardiac function spontaneously recovers and infection control can be achieved using antibiotics or drainage. The present study showed that myocardial injury severity as evaluated by peak troponin I level was associated with a lower risk of in-hospital mortality. These findings suggest that serial monitoring of left ventricular ejection fraction and troponin I level may help differentiate patients with the component of severe cardiogenic dysfunction from those with the distributive component during refractory septic shock. This hypothesis should be tested in a well-designed prospective trial or one with a large data registry.

One of the most important issues for patients on ECMO for refractory septic shock is multiple organ failure, which was the leading cause of death in our study. The baseline SAPS 3 and SOFA scores were similar between the survivor group and the non-survivor group. However, SOFA score at Day 3 (15 vs 18, P = 0.01) and the difference between two subsequent SOFA scores (1 vs 4, P = 0.04) were significantly different between the two groups. The trend in SOFA score over time could be used to reflect patient response to ECMO support and offer an objective evaluation of treatment response [25]. This change could facilitate decision-making regarding the appropriateness of organ support.

Our study had several limitations. First, our study presents a single-centre experience regarding the use of ECMO in adults with refractory septic shock. The number of enrolled patients is not sufficient to infer definite conclusions from this study, but it may help in generating hypotheses on which further research may be based. Secondly, we could not evaluate the criteria for selection of patients for ECMO among all septic patients because we extracted adult patients with refractory septic shock from the hospital-based registry of ECMO-supported patients. In this setting, we were not able to exactly determine why the physicians made certain decisions. Thirdly, selection biases for the initiation of mechanical-assist devices might exist because the attending physician in charge made the decision to use ECMO. However, randomization of ECMO in patients with septic shock refractory to conventional treatments is not possible and is unethical. Instead, a well-organized protocol outlining patient selection, monitoring of predictors and management of ECMO will be needed to control this potential bias. Since there have been few clinical studies regarding the use of ECMO in patients with refractory septic shock, our study provides additional information about such circumstances. A multicentre registry study or prospective cohort study, however, is needed for a more complete assessment of the role of ECMO in refractory septic shock.

In conclusion, survival to hospital discharge of adult patients with refractory septic shock remains low in spite of ECMO support. Our findings suggest that the implantation of ECMO during refractory septic shock could be considered in patients with severe myocardial injury and avoided in patients who have received CPR.

Conflict of interest: none declared.

REFERENCES


Table 4: Independent predictor of in-hospital mortality determined by univariable and multivariable Cox proportional hazard regression models

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0.52 (0.20–1.31)</td>
<td>0.16</td>
</tr>
<tr>
<td>SOFA score, baseline</td>
<td>1.27 (1.08–1.50)</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak troponin I</td>
<td>0.99 (0.97–1.00)</td>
<td>0.13</td>
</tr>
<tr>
<td>Peak troponin I &gt; 15 ng/ml</td>
<td>0.40 (0.14–1.11)</td>
<td>0.08</td>
</tr>
<tr>
<td>CPR</td>
<td>3.08 (1.30–7.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>CPR duration</td>
<td>1.02 (1.00–1.04)</td>
<td>0.06</td>
</tr>
<tr>
<td>Model 1: multivariable model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR</td>
<td>4.61 (1.55–13.69)</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak troponin I &gt; 15 ng/ml</td>
<td>0.34 (0.12–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 2: model 1 + CPR duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR duration, min</td>
<td>1.02 (1.00–1.04)</td>
<td>0.04</td>
</tr>
<tr>
<td>SOFA score, baseline</td>
<td>1.35 (1.01–1.81)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Multivariable models adjusted by backward elimination.

*a Model 1 adjusted for age, chronic kidney disease, SOFA score, CPR, peak troponin I (>15 ng/ml), renal replacement therapy and appropriate antibiotic therapy.

*b Model 2 further adjusted for CPR duration.

CI: confidence interval; CPR: cardiopulmonary resuscitation; SOFA: Sepsis-related Organ Failure Assessment.