Renal function and survival in 200 patients undergoing ECMO therapy

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Abstract
Background. Extracorporeal membrane oxygenation (ECMO) is increasingly used in the intensive care unit (ICU) setting to improve gas exchange in patients with acute respiratory distress syndrome as well as in patients pre- and post-heart and lung transplantation. In this clinical setting, acute kidney injury (AKI) is frequently observed. So far, it is unknown how AKI affects the survival of critically ill patients receiving ECMO support and whether veno-venous and veno-arterial ECMO have different effects on kidney function.

Methods. This is a retrospective analysis of patients undergoing ECMO treatment in medical and surgical ICUs in a tertiary care centre. We evaluated all patients undergoing ECMO treatment at our centre between 1 January 2005 and 31 December 2010. Data from all 200 patients (83F/117M), median age 45 (17–83) years, were obtained by chart review. Follow-up data were obtained for up to 3 months.

Results. Three-month survival of all patients was 31%. Of the 200 patients undergoing ECMO treatment, 60% (120/200) required renal replacement therapy (RRT) for AKI. While patients without RRT showed a 3-month survival of 53%, the survival of patients with AKI requiring RRT was 17% (P = 0.001). Longer duration of RRT was associated with a higher mortality.

Conclusions. AKI requiring RRT therapy in patients undergoing ECMO treatment increases mortality in ICU patients. Future studies have to clarify whether it is possible to identify patients who benefit from the combination of ECMO and RRT.

Keywords: AKI; ECMO; extended dialysis; renal function

Introduction

In 1972, Hill et al. [1] reported on the first successful use of extracorporeal membrane oxygenation (ECMO) in a patient with adult respiratory distress syndrome (ARDS). In the following years, this technique improved and now represents a mainstay of intensive care therapy in many tertiary care centres around the world with a peak in interest in the recent H1N1 influenza pandemic [2]. According to the ‘Extracorporeal Life Support Organization’ (http://www.elso.med.umich.edu/Publications.html), more than 40 000 patients worldwide have been treated with ECMO for the temporary management of pulmonary or heart failure, for patients with ARDS [3] and as a bridge to recovery or bridge to transplantation [4]. ECMO enables an efficient oxygenation and elimination of carbon dioxide. It can be operated in two different modes, in a venovenous (VV) (mainly for ventilatory failure) or veno-arterial (VA) (providing both respiratory and cardiac support) configuration. The use of ECMO is demanding and expensive as it requires a highly skilled staff and specialized equipment and should therefore be reserved for those patients with extremely severe but potentially reversible condition, or for transplantation candidates, respectively. Acute kidney injury (AKI) is a major comorbid condition in patients undergoing extracorporeal ventilatory support, even in pumpless systems for CO₂ elimination [5]. In the critically ill patient not treated with ECMO, AKI is associated with high mortality rates of 60% [6]. The rate of RRT dependence in patients treated with ECMO ranges between 2% in bypass surgery patients [7] and 65% in patients treated for refractory postcardiotomy cardiogenic shock [8]. In a small study involving 46 patients in cardiogenic shock undergoing ECMO therapy, the hospital mortality of the 11 patients who also required RRT was 100% [9]. So far, it is unknown, what impact the dependence from RRT has on the survival of other critically ill patients that undergo ECMO treatment. For those patients not receiving RRT dependently, it is not known whether improvement of either oxygenation or circulating blood volume has any impact on renal function. Our retrospective cohort study was aimed at addressing these two questions.
Materials and methods

This retrospective cohort study included all adult patients who underwent ECMO treatment from 1 January 2005 to 31 December 2010 in a tertiary care university hospital. The study was conducted in accordance with the guidelines of the internal review board. A total of 200 patients were identified in the central documentation system of the hospital. From all of those, patient charts as well as laboratory data were reviewed. AKIN stage 3 was defined as necessity for renal replacement therapy (RRT). RRT was exclusively performed by extended dialysis (ED). All patients requiring RRT in addition to ECMO treatment received ED using the GENIUS system. Details of the system are summarized elsewhere [10].

Demographic and clinical data were collected from the hospital records, including gender, age, diagnosis, time until the appearance of renal failure and hospital mortality. The laboratory information was obtained from a computer database. The study endpoints were the day of demise or discharge from hospital.

The Simplified Acute Physiology Score II [SAPS II; excluding the Glasgow Coma Scale (GCS)] was observed for the first 24 h and only the worst values were used for the calculation of the score. The measurement has been completed and resulted in an integer point score between 0 and 163 and a predicted mortality between 0 and 100% [12].

**Horowitz index**

The Horowitz index is defined as the ratio of arterial oxygen partial pressure (paO2) and the concentration of oxygen in the inhaled air (FiO2). The normal Horowitz index ranges between 350 and 450, while a value below 300 is indicative of a moderately severe lung injury (acute respiratory distress syndrome). A value below 200 shows a severe lung injury (acute lung injury).

**Statistical analysis**

Descriptive analysis was performed using medians and inter-quartile ranges. All statistical parameters were tested for normal distribution using the Shapiro-Wilk test of normality. Discrete variables were compared using Pearson’s χ² test or Fisher’s exact test. For normally distributed data, continuous variables of patients with and without RRT were analysed using the Welch two-sample t-test. Otherwise, the Wilcoxon rank-sum test was used. The probability of survival was determined on the basis of survival curves using the Kaplan-Meier method. Differences between the groups were calculated using a stratified log-rank test (Fleming-Harrington G familly). Hazard ratios for the development of RRT as a time-dependent variable were evaluated by using a Cox proportional regression model. Last survival status for all patients was assessed on 31 March 2011. Two-sided P-values of <0.05 were considered statistically significant differences. R-Project software version 2.10.1 for Linux was used for statistical computation.

Results

We identified 200 patients undergoing ECMO treatment within our observation period. Patient characteristics are presented in Table 1. More than a half (n = 120, 60%) of all patients required RRT. One-quarter of these patients had already been dialysis-dependent before ECMO insertion (n = 27; 23%). Together with the 22 patients who became dialysis-dependent on the day of ECMO insertion, almost half were dialysis dependent at that time point. Within 2 days after ECMO placement, another 24 patients were in need of RRT. Hence, within 7 days after ECMO insertion, 74% (n = 87) of RRT-dependent patients were on ED (Figure 1). Patients undergoing RRT were not different with respect to gender, age, weight, paO2, paCO2 and the Horowitz index when compared with those without need for RRT. However, the patients undergoing RRT had a statistically significantly higher SAPS score, a higher creatinine on admission and a higher percentage of pre-existing renal failure than those not requiring RRT (Table 1).

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**Table 1. Patient characteristics before ECMO insertion (unless otherwise stated)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 200)</th>
<th>RRT-dependent (n = 117)</th>
<th>Without RRT (n = 83)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.0</td>
<td>46.0</td>
<td>45.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>117 (59)</td>
<td>76 (65)</td>
<td>41 (49)</td>
<td>0.03</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170</td>
<td>174</td>
<td>74.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.0</td>
<td>74.0</td>
<td>69.5</td>
<td>0.37</td>
</tr>
<tr>
<td>SAP score</td>
<td>44.0</td>
<td>46.0</td>
<td>40.0</td>
<td>0.03</td>
</tr>
<tr>
<td>FiO2</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.66</td>
</tr>
<tr>
<td>paO2</td>
<td>88.0</td>
<td>88.0</td>
<td>86.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Horowitz index</td>
<td>100.0</td>
<td>107.5</td>
<td>95.2</td>
<td>0.49</td>
</tr>
<tr>
<td>pH</td>
<td>7.27</td>
<td>7.25</td>
<td>7.29</td>
<td>0.08</td>
</tr>
<tr>
<td>paCO2</td>
<td>53.0</td>
<td>50.0</td>
<td>56.0</td>
<td>0.18</td>
</tr>
<tr>
<td>HCO₃</td>
<td>22.0</td>
<td>22.0</td>
<td>24.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactate</td>
<td>3.4</td>
<td>3.4</td>
<td>3.3</td>
<td>0.59</td>
</tr>
<tr>
<td>Na⁺</td>
<td>141.0</td>
<td>141.0</td>
<td>142.5</td>
<td>0.52</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.5</td>
<td>4.6</td>
<td>4.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Pre-existing renal insufficiency [n (%)]</td>
<td>77 (38.5)</td>
<td>71 (60.7)</td>
<td>6 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, admission (µmol/L)</td>
<td>98.0</td>
<td>104.0</td>
<td>74.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine, ECMO d1₄⁺</td>
<td>107.0</td>
<td>123.0</td>
<td>89.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, ECMO d7₄⁺</td>
<td>95.5</td>
<td>114.0</td>
<td>70.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Veno-venous ECMO [n (%)]</td>
<td>111 (55.5)</td>
<td>56 (47.9)</td>
<td>55 (66.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Veno-arterial ECMO [n (%)]</td>
<td>89 (44.5)</td>
<td>61 (52.1)</td>
<td>28 (33.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal replacement therapy (RRT) [n (%)]</td>
<td>117 (58.5)</td>
<td>117 (100)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRT pre-ECMO</td>
<td>25 (12.5)</td>
<td>25 (21.4)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transplant patients [n (%)]</td>
<td>74 (37.0)</td>
<td>52 (44.4)</td>
<td>22 (26.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>31</td>
<td>17</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Creatinine only from patients without ED dependence.

Log-rank analysis.
The 90-day survival of the whole cohort was 31%. While patients undergoing RRT exhibited a 90-day survival of 17%, those not requiring RRT had a 90-day survival of 53% (Figure 2). The overall survival of transplant patients receiving ECMO and RRT was comparable to the whole population (16 versus 15%). Patients undergoing ECMO therapy as a bridge to transplantation showed a 90-day survival of 57%. Patients who remained on the waiting list without an organ available had only a 90-day survival of 18% (Figure 3). Stepwise transformation of multivariate regression model with exclusion of non-predictive covariates consistently reveals robust P-values of RRT and its significant impact on survival (Table 2). However, analysis of hazard for RRT was not proportional, i.e. varied over time. Figure 4 confirms and suggests that RRT may have non-proportional hazard over time. It appears that the risk of death for RRT constantly increases over time and has strong predictive power for survival in the second half of the study period (18-fold increase in death by Day 38).

Discussion

The pertinent findings of our study were that (i) the combination of ECMO treatment and RRT is associated with a high mortality; (ii) most of the patients with this combination were either dialysis dependent before the start of ECMO treatment or within 48 h after start of ECMO therapy, (iii) the risk of death for RRT increases over time and (iv) successful transplantation was associated with the best survival within this cohort.

The effect of RRT on the outcome of ECMO patients

The overall survival in our cohort was 31%. While patients without the need for RRT showed a 98-day survival of 53%, patients with RRT had an overall survival of 17%. Hence the need for RRT in patients receiving ECMO support is associated with an extraordinary increase mortality. This is not surprising since it is known that any additional organ failure has detrimental effect on the outcome of critically ill patients, and the need for RRT may reflect inadequate renal perfusion or direct injury to
the kidney either due to disease process itself or due to ECMO-associated side effects (haemolysis, multiple transfusion, etc.). Our data are in line with recent observations that showed that the need for dialysis during ECMO therapy was an independent predictor of mortality [13]. Wu et al. [14] identified the need for RRT as an independent risk factor associated with failure to wean from ECMO and mortality (odds ratio = 7.2 for mortality if renal replacement happened before or within 72 h after initiation of ECMO). Further, in a large cohort of 7941 neonates and 5766 children on ECMO, AKI and RRT were independently associated with mortality and their single presence doubled the odds of dying after adjusting for all confounding variables [15]. Post-cardiotomy, ECMO-supported children requiring haemofiltration were five times more likely to die [16]. In adults, the negative prognostic role of acute renal failure has been demonstrated in relatively large studies employing post-cardiotomy patients [8] as well as patients requiring ECMO for circulatory support. The fact that outcome is worse in a given acutely ill patient population if AKI necessitating RRT develops is of course not exceptional and has been depicted in many populations (for review see Lameire et al. [17]). Indeed, patients who needed both ECMO and RRT were sicker as reflected by disease severity scores, a difference, however, mainly caused by the deteriorating renal function.

**Occurrence of AKI in regard to initiation of ECMO therapy**

To our knowledge, the exact timing of the start of RRT in ECMO patients has never been investigated before. Most of the ECMO patients became RRT dependent within 48 h of ECMO insertion. Bagshaw et al. [18] described that a late start of RRT [relative to intensive care unit (ICU) admission] was associated with greater mortality. In our cohort, patients who required RRT later (relative to the time of ECMO insertion), and for a longer period of time, had a higher risk of death. Prospective investigations in this patient cohort have to clarify whether early initiation of RRT would have an effect on survival.

**Mode of ECMO and renal function**

Preclinical data suggested that respiratory acidosis induces a drop in GFR, effective renal plasma flow and urine output [19]. Accordingly, we assumed that amelioration of respiratory acidosis would improve renal function. This was however not the case. Patients receiving ECMO but not RRT exhibited no reduction in serum creatinine comparing the day of ECMO insertion with the day after starting ECMO treatment. There was also no difference between the veno-venous and the veno-arterial mode of ECMO therapy in this regard.

**Limitations of the study**

We wish to point out limitations of our study. First, the retrospective design and the single-centre setting are important limitations, yet we included patients from different departments, i.e. surgical and medical, into the analysis. Last but not least, we did exclude patients on interventional lung support, as those had been reported previously [5].

**Conclusion**

The combination of ECMO treatment with AKI requiring RRT dramatically increases mortality. Most of the patients who become dialysis dependent do so within 48 h of ECMO insertion. These patients already have an impaired renal function at the time of ICU admission. The best outcome in our cohort could be obtained in patients who were successfully bridged to (lung) transplantation.

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Conflict of interest statement. None declared.

**References**

13. Lan C, Tsai PR, Chen YS et al. Prognostic factors for adult patients receiving extracorporeal membrane oxygenation as mechanical circulatory support—a 14-year experience at a medical center. *Artif Organs* 2010; 34: E59–E64

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