Extracorporeal membrane oxygenation to support adult patients with cardiac failure: predictive factors of 30-day mortality

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Abstract

Adult patients supported on extracorporeal membrane oxygenation (ECMO) are very sick and many complications are often present in each single patient; therefore, it is not always easy to find some risk factors that can predict the early outcome. This retrospective study reports our experience in ECMO support treatment in adult cardiac patients suffering from cardiac failure (CF) in which one or more predictive factors of 30-day mortality were analyzed. Between January 2002 and August 2009, 42 consecutive adult cardiac patients with cardiogenic shock (mean age 64.3 ± 11.3 years) were supported on ECMO for >2 days. They were divided into patients who had a survival <30 days (n = 20) and patients who survived >30 days (n = 22). Twenty-nine patients (69%) survived on ECMO. Sixteen patients were discharged with a survival rate of 38.1%. The overall mean ECMO duration was 7.9 ± 5.3 days. The following variables were significantly different between the two groups: number of platelets and packed red blood cells (PRBCs) transfused per day during ECMO (P = 0.002 and P = 0.003), blood lactate levels 48 h and 72 h after the initiation of ECMO (P = 0.01 and P = 0.04), indexed blood flow after 48 h and 72 h (P = 0.01 and P < 0.0001), liver failure (P = 0.001) and multiorgan failure (P = 0.002). Stepwise logistic regression identified that blood lactate levels at 48 h and number of PRBCs transfused were associated with 30-day mortality (P = 0.019, odds ratio (OR) = 2.16; 95% confidence interval (CI) = 1.13–4.14 and P = 0.008, OR = 1.08; 95% CI = 1.02–1.14, respectively). The predicted probability of mortality would be 52% when blood lactate levels are >3 mmol/l after 48 h. The blood lactate level at 48 h and PRBCs transfused per day can be considered as important parameters to predict the mortality in adult cardiac patients supported by ECMO for CF.

Keywords: Extracorporeal membrane oxygenation; Heart failure; Postinfarction cardiac complication

1. Introduction

Veno-arterial extracorporeal membrane oxygenation (ECMO) is considered a valuable tool to support children [1, 2] and patients suffering from severe respiratory insufficiency [3] and results in the short- and medium-term are encouraging [4, 5]. In adult cardiac patients, the ECMO is useful for cardiac failure (CF) that complicates 7–10% of patients with acute myocardial infarction [6] and for refractory postcardiotomy syndrome that occurs in 0.5–5% of patients who underwent cardiac surgery operation; in both groups of patients the primary diseases that caused CF have a high mortality rate, ranging from 75% to 90% [7]. However, the use of ECMO for supporting adult patients with CF is still not widely considered and negative short-term results are still reported [8]. In July 2009, the Extracorporeal Life Support Organization (ELSO) reported the data of the international summary of Extracorporeal Life Support (ECLS) registry. In this report, the percentage of survival to ECLS and survival to discharge for cardiac patients are 48% and 34%, respectively; survival to ECLS and survival to discharge for patients suffering from cardiac arrest is 36% and 27%, respectively.

The adult patients supported with cardiac ECMO are in a very compromised hemodynamic situation and many of the complications are often present in each individual patient, such as bleeding, infection, low peripheral perfusion, low splanchnic perfusion, acute renal failure, so it is difficult to predict short-term results. In this retrospective study, we aimed to find one or more predictors of 30-day mortality. These predictors could be useful to make a individualized decision and to proceed with further treatment for each patient in a subset of ECMO patients supported for 48 h.

2. Materials and methods

2.1. Patient characteristics

Although all patients in our study had different indications for ECMO support, in each patient the initial etiology has led to refractory cardiogenic shock (CS) with a predicted
mortality ranging from 75% to 90% [8]. Between January 2002 and August 2009, 42 consecutive adult cardiac patients (mean age 64.3 ± 11.3 years, ranging from 41 to 83 years; 28 males, 66.7%) were supported with ECMO for > 48 h for the treatment of CF. We decided to exclude all the patients who were supported < 48 h (eight patients) because they did not meet the inclusion criteria. In our Institution, the inclusion criteria for ECMO support were primary CS that does not respond to multiple inotropic agents and/or intra-aortic counterpulsation (IABP), failure when being weaned off cardiopulmonary bypass (CPB) and postcardiotomy syndrome; exclusion criteria were considered irreversible brain damage, terminal malignancy, renal failure on dialysis and cardiac arrest not witnessed. Age > 75 years was considered a relative contraindication to ECMO support, and any patient in this age group had a brief and rapid assessment before starting the ECMO. In this group of patients, the decision to initiate ECMO was always taken by the ECMO team. In practice, if the patient has no apparent underlying disease and or irreversible or severe brain disease, he/she is considered for ECMO support. Seventeen patients (40%) were supported on ECMO for primary CS due to extensive acute myocardial infarction and 15 of them underwent surgery. Fourteen patients (33.3%) were supported on ECMO for failure when being weaned off CPB. Eleven patients (26.2%) received the ECMO support for postcardiotomy CS. One patient received ECMO support for asystolia following tamponade syndrome occurring on the 6th postoperative day.

Patients were divided into two groups: patients who had a survival of < 30 days (< 30 days group; n = 20) and patients who survived > 30 days (> 30 days group; n = 22).

2.2. ECMO circuit and management

The ECMO circuit and management were already described [9]. In brief, the Permanent Life Support (PLS) ECMO circuit loop consists of a Quadrox D oxygenator and a centrifugal pump Rotaflow (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany). Veno-arterial peripheral femoral cannulation was used in 27 patients (64.3%). The rest of the patients received a central cannulation or mixed through the ascending aorta and right atrium or ascending aorta and the femoral vein, respectively. Tubing, pump and oxygenator were all coated with Bioline® Coating. Priming the circuit usually requires 4–5 min and this was shown to be very useful in those patients who require immediate ECMO support in other hospital sites, such as intensive care units, emergency rooms and hemodynamic laboratory. ECMO blood flow has been optimized during the first 24–48 h in order to maintain a cardiac index of 2.5 l/min/m², a mixed venous oxygen saturation (SvO₂) of about 70% and a mean blood arterial pressure of 60–70 mmHg. All ECMO circuits had a heat exchanger. Five thousand IU of heparin were administered 5 min before the femoral arterial cannulation in patients with peripheral cannulation. In patients with postcardiotomy syndrome, administration of heparin was stopped until the bleeding was decreased significantly by mediastinal drainage. During the ECMO, continuous intravenous heparin was administered to obtain an activate clotting time of 140–160 s and a prothrombin time value of 50–60 s. Infusion of antithrombin III (AT III) was required if the AT III serum level was below 80%. In patients with a motionless left ventricle, small doses of inotropes (dobutamine) were given to prevent the formation of the clot inside the left ventricle. Those patients who had had a cardiac arrest before starting with ECMO were gradually cooled to 32–34 °C during the first 24–36 h. Multiple heart examinations by transesophageal echo were performed to assess the left ventricle motion. To prevent limb ischemia, in 10 patients (23.8%) the distal perfusion has been optimized through an 8 Fr catheter introduced distally to the cannulation site and connected to the side-arm of return arterial cannula. All patients needed blood transfusions in order to maintain a hematocrit of 30–35% and platelets were infused when the platelet count was < 50,000–60,000/μl. Mechanical ventilation was continued throughout the ECMO support with the same management for every patient. Ventilator settings were commonly set at a tidal volume of 8 ml/kg, 4 breaths/min, positive end expiratory pressure of 10 cm H₂O and FiO₂ of 0.40–0.60. IABP was employed in 25 patients (73.5%) with the objective of reducing the afterload, to improve the coronary and cerebral perfusion and to maintain a pulsatile flow. The use of IABP is not considered when contraindications, such as aortic aneurysm or severe peripheral arterial disease occur. The IABP was inserted within 1 h after the initiation of the ECMO in those patients who had no aortic counterpulsation before the support.

No attempt to wean off ECMO was considered during the first 48 h. Step by step is our main strategy for weaning ECMO using transesophageal echocardiography monitoring. This consists of reducing the pump flow to 1.0 l/min/m² for about 40–60 min having obtained an ACT of 180 s. In patients who were supported with IABP, this device was set to 1:1. If the hemodynamics remained stable without the addition of inotropes, heparin was stopped and ECMO was removed at the bedside or in the operating room within the next few hours. No patient after ECMO removal needed to be supported again with a longer ECMO run.

2.3. Blood sample and data collection

Blood lactate level, total creatine-kinase (CK), isoenzyme MB of CK (CK-MB), CK-MB relative index as the ratio of CK-MB to total CK, platelet cells count and blood GPT level were collected at pre-ECMO time, at 24, 48 and 72 h after ECMO initiation in both groups. Indexed blood flow of the centrifugal pump (l/min) was recorded at 4, 24, 48 and 72 h after ECMO initiation.

2.4. Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation (S.D.). A P-value < 0.05 was considered to have a statistical significance. Categorical variables are presented as percentages and χ²-test were used to compare them. Analysis of variance for repeated measures was employed for numerical variables measured during the time, such as platelet counts, blood lactate levels, CK-MB values and CK-MB relative index. In case of significance, the Bonferroni post hoc test was then used. Continuous variables were
evaluated by Student t-test for independent variables. An univariate analysis was used as a screening process in order to identify any possible predictor variables, which were chosen as those with P<0.05. Stepwise logistic regression analysis was applied to determine the independent predictors of 30-day mortality. A scatter graphic was then built to highlight the correlation between predicted probability of mortality and values of blood lactate. Kaplan–Meier survival curve with log-rank test was used to compare the survival at 30 days. All statistic analyses were performed with the Statistical Package for Social Science (SPSS, version 15.0 for Windows; SPSS Inc, Chicago, IL, USA). A post study sample size calculation was done. From our study, the mean±S.D. level of blood lactate at 48 h in the <30 groups and ≥30 days group were 3.94±2.85 and 2.26±0.88, respectively. Using these estimates, the number of patients required in each arm is 19 for a two-sided test with α =0.05 and power of 80%. We had 20 and 22 patients in the <30 days group and the >30 days group, respectively, which more than met the required sample size.

3. Results

Demographic data and clinical pre-ECMO features of both groups are summarized in Table 1. The presence of diabetes and the use of IABP were statistically different in both groups. The intraoperative and postoperative parameters are shown in Table 2. Twenty-nine patients (69%) were weaned off ECMO. Among them, 16 patients (38.1%) survived to hospital discharge. Thirteen patients (31%) died during ECMO. Among these patients, in six cases (14.3%) the ECMO was withdrawn by criteria of futility (i.e. brain death, motionless heart). The ECMO was inserted in the operating room (n=21; 50%), the postoperative intensive care unit (n=10; 23.8%), the catheterization laboratory (n=9; 21.4%) and the emergency room (n=2; 4.8%). The mean time from the decision to initiation of ECMO was 43 min±19 min (range 21–75 min). The indications and the types of operations are listed in Table 3. Causes of all deaths are reported in Table 4. Fifteen patients had IABP inserted after ECMO initiation. In those patients with the IABP before the cardiac support, the ECMO was started after an overall mean time of 11±7 h (range 3–24 h) without differences between the two groups.

As for the ECMO complications, there were statistically significant differences between the two groups for the onset of liver failure (P<0.001), for the number of platelet and packed red blood cells (PRBCs) units transfused per day during ECMO (P<0.002 and P<0.04, respectively), and for the duration of intubation (P<0.005) due to shorter duration of survival. As shown in Fig. 1, levels of lactate in the blood decreased in both groups but the level of blood lactate remained significantly higher in the <30 days group compared to the >30 days group at 48 h (P<0.013) and at 72 h (P<0.0001). Moreover, as shown in Fig. 2, indexed blood flow was statistically higher in the <30 days group

### Table 1

Demographic data and pre-ECMO clinical features

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Group &lt;30 days (n=20)</th>
<th>Group &gt;30 days (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.3±11.3</td>
<td>64.8±9.6</td>
<td>63.8±12.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>28 (66.7%)</td>
<td>14 (70%)</td>
<td>14 (63.6%)</td>
<td>0.66</td>
</tr>
<tr>
<td>BMI</td>
<td>26.1±4.4</td>
<td>25.6±4.3</td>
<td>26.2±4.6</td>
<td>0.46</td>
</tr>
<tr>
<td>EF (%)</td>
<td>21.3±13.3</td>
<td>19.4±12.6</td>
<td>23.1±14.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (66.7%)</td>
<td>15 (75%)</td>
<td>13 (59%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (33.3%)</td>
<td>11 (55%)</td>
<td>3 (13.6%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Lipidic disorder</td>
<td>17 (40.5%)</td>
<td>7 (35%)</td>
<td>10 (45.5%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/100 ml</td>
<td>4 (9.5%)</td>
<td>3 (15%)</td>
<td>1 (4.5%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Left main &gt; 70%</td>
<td>10 (23.8%)</td>
<td>3 (15%)</td>
<td>7 (36.8%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of diseased coronaries</td>
<td>2.4±0.7</td>
<td>2.3±0.8</td>
<td>2.4±0.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Primary CS</td>
<td>17 (40%)</td>
<td>6 (42.1%)</td>
<td>9 (40.9%)</td>
<td>0.93</td>
</tr>
<tr>
<td>IABP before ECMO</td>
<td>15 (35.7%)</td>
<td>4 (20%)</td>
<td>11 (50%)</td>
<td>0.04</td>
</tr>
<tr>
<td>CPR</td>
<td>21 (50%)</td>
<td>7 (35%)</td>
<td>14 (63.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Log EuroSCORE (%)</td>
<td>25.5±21</td>
<td>27±23.8</td>
<td>24.1±18.5</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Note:** BMI, body mass index; EF, ejection fraction; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenator; IABP, intra-aortic counterpulsation; CPR, cardiopulmonary resuscitation.
Table 3

<table>
<thead>
<tr>
<th>Indications for ECMO</th>
<th>Total (n=42)</th>
<th>Types of operation</th>
<th>Total (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CAD</td>
<td>19</td>
<td>CABG</td>
<td>16</td>
</tr>
<tr>
<td>CAD + valve disease</td>
<td>10</td>
<td>CABG + AVR</td>
<td>3</td>
</tr>
<tr>
<td>Isolated valve disease</td>
<td>4</td>
<td>CABG + LFWR</td>
<td>1</td>
</tr>
<tr>
<td>CAD + LFWR</td>
<td>1</td>
<td>CABG + MVA</td>
<td>4</td>
</tr>
<tr>
<td>CAD + valve disease + LFWR</td>
<td>1</td>
<td>CABG + MVA + AVR</td>
<td>1</td>
</tr>
<tr>
<td>LFWR</td>
<td>1</td>
<td>CABG + MVA + LFWR</td>
<td>1</td>
</tr>
<tr>
<td>Massive pulmonary embolism</td>
<td>2</td>
<td>CABG + MVR + AAR</td>
<td>1</td>
</tr>
<tr>
<td>Type A aortic dissection</td>
<td>1</td>
<td>LFWR</td>
<td>1</td>
</tr>
<tr>
<td>Postinfarction VSD rupture</td>
<td>3</td>
<td>MVA</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MVR</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MVR + AVR</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No procedure</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTCA</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary embolectomy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type A aortic dissection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic VSD closure</td>
<td>3</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; AVR, aortic valve replacement; LFWR, left free wall rupture; MVA, mitral valve annuloplasty; AAR, ascending aorta replacement; MVR, mitral valve repair; VSD, ventricular septal defect; CAD, coronary artery disease.

compared to the >30 days group at 48 h (P=0.001) and at 72 h (P=0.001). ECMO duration and IABP balloon duration were similar in both groups. The variables with a P<0.05 (diabetes, use of IABP before ECMO, duration of intubation, multiorgan failure (MOF), liver failure, PRBCs per day, platelets per day, fresh frozen plasma (FFP), blood lactate levels at 48 and 72 h, indexed blood flow at 48 and 72 h) selected using the univariate logistic analysis were then introduced in the stepwise logistic regression analysis which revealed that blood lactate levels at 48 h after initiation of ECMO and number of PRBCs transfused per day are independent predictors of mortality during ECMO support [P=0.019, odds ratio (OR)=2.16; 95% confidence interval (CI)=1.13–4.14 and P=0.04, OR=2.54; 95% CI=1.02–6.41, respectively]. As shown in Fig. 3, when the level of lactate in blood has a value of 3 mmol/l after 48 h the ECMO support initiation, the predicted probability of mortality would be 52%. Depending on the value of blood lactate level ≥3 mmol/l at 48 h of ECMO, we have further divided the patients into two groups (blood lactate <3 mmol/l, n=28 and blood lactate >3 mmol/l, n=14). Following the Kaplan–Meier analysis, those patients with blood lactate levels >3 mmol/l at 48 h, had a worse survival compared those patients with a value <3 mmol/l (14.3±9.4% vs. 54.8±10%; P=0.001). Regarding blood transfusions, we did not find any statistical correlation between number of PRBCs transfused per day and ECMO duration (R=0.24, P=0.11). Limb ischemia occurred in five patients per group. All these patients had a peripheral arterial perfusion. Ischemia was promptly addressed and resolved through the use of a reperfusion line. No differ-

Table 4

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Total (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain death</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1</td>
</tr>
<tr>
<td>Fulminant peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>14</td>
</tr>
<tr>
<td>Motionless heart</td>
<td>1</td>
</tr>
<tr>
<td>Acute respiratory Insufficiency</td>
<td>1</td>
</tr>
<tr>
<td>Untractable hemorrhagia</td>
<td>2</td>
</tr>
</tbody>
</table>
ence was noted between the two groups endless levels of blood lactate during the first three days of ECMO support.

4. Discussion

The main findings of our study are: (a) when the blood lactate level is \( > 3 \text{ mmol/l} \) at 48 h after beginning ECMO, the 30-day mortality is increased, with an expected probability of mortality of 52% and (b) the number of PRBCs transfused was significantly higher in patients who died within 30 days.

As reported by the ELSO registry data of 2009, during the last decades the use of ECMO support is steadily increasing with an overall survival using ECMO support in patients with CF of 34% and ECMO weaning rate of 48%.

At the moment, there are no specific guidelines for the management of ECMO and the decision to discontinue support is still a challenge and is entrusted to the experience of each center. Hyperlactatemia (level of blood lactate above 3 mmol/l) during CPB is associated with increased mortality and morbidity, and appears to be related primarily to a state of inadequate perfusion [10]. In our study, we observed that patients who survived to 30 days showed a significantly lower level of blood lactate at 48 and 72 h than non-survivors. At the same time, for patients who survived to 30 days, the blood flow of the pump was lower compared to the other group. The trend of blood lactate could be a demonstration that all patients with blood lactate levels \( > 3 \text{ mmol/l} \) during the first three days of support suffered from a low organ perfusion, despite an apparently optimized indexed blood flow. By logistic regression analysis, it was clearly confirmed that the blood lactate level after 48 h is a parameter to predict the probability of 30-day mortality, i.e. 52% in cases where the level of lactate in blood is \( \geq 3 \text{ mmol/l} \). Zhang et al. [11] observed that patients who presented an index of CK-MB at 48 h \( > 11.26\% \) should have a predicted probability of mortality of 50% and patients not weaned off ECMO have a CK-MB relative index significantly higher than patients who are weaned off. In our experience, we found that the CK-MB relative index was dramatically reduced in both groups at 24, 48 and 72 h without significant differences observed between the two groups. For this reason, we have not considered this index as the sole predictor of mortality.

In the literature different and sometimes contradictory interpretations of the values of blood lactate are reported. Chen et al. [6] recently reported that patients who were weaned off ECMO but died within 30 days had pre-ECMO blood lactate levels significantly higher than patients who survived ECMO. In our study, however, we did not find any statistical difference between the two groups regarding the levels of lactate in the blood before starting ECMO. Ko et al. [12] reported no statistically significant difference regarding the level of lactate in the blood 24 h after beginning ECMO among the three groups of patients (died on ECMO, weaned but died, weaned and survived). Recently, Bakhtiary et al. [8] did not show any significant difference regarding the levels of lactate in the blood after 72 h of initiation of ECMO between survivors and non-survivors. Luo et al. [13] failed to detect statistically significant differences between survivors and non-survivors with regard to blood lactate levels after 24 h of ECMO initiation, but they did not report further data on the levels of blood lactate at 48 and 72 h.

Some authors have reported that the majority of blood transfusions in adult patients were during ECMO [14] and the need for transfusions was associated with the loss of hemoglobin and platelet counts due to the high incidence of bleeding as a result of the continuous heparinization and associated thrombocytopenia, hemolysis and hemodilution that are related to the duration of ECMO [15]. On the basis of these data, in our study we focused also on the need for transfusions during ECMO, but we were unable to demonstrate a positive correlation between the number of PRBCs transfused per day and the duration of ECMO. One possible interpretation of this result is that during ECMO, the need for transfusion is still high but extremely variable from case to case, because in some patients the bleeding is mainly due to the surgery and the central cannulation rather than the sole result of contact between blood and the circuit.

In conclusion, the level of lactate in the blood is easy to measure and is a very useful parameter that should be considered as one of the vital parameters to be checked frequently during ECMO support. Time evaluation of the level of blood lactate at 24, 48, 72 h would be useful for the clinicians to predict the outcome at 30 days; in addition, the rate of bleeding and the need for blood transfusions during ECMO remain high and are associated with an increase in mortality. Further studies are necessary and advisable in the near future to provide a valid score for predicting mortality in all adult cardiac patients supported by ECMO for refractory CS.

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References


