Extracorporeal membrane oxygenation for acute respiratory distress syndrome: is the configuration mode an important predictor for the outcome?

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Abstract

Extracorporeal membrane oxygenation (ECMO) is increasingly applied as rescue-therapy for patients with severe acute respiratory distress syndrome (ARDS). Here, we evaluate the effect of different configuration strategies (venovenous vs. venoarterial vs. veno-venoarterial) on the outcome. From 2006 to 2008, 30 patients received ECMO for severe ARDS. Patients were divided into three groups according to the configuration: venovenous (vv; n = 11), venoarterial (va; n = 8) or veno-venoarterial (vva; n = 11). Data were prospectively collected and endpoint was 30-day mortality. To identify independent risk factors, univariate analysis was performed for clinical parameters, such as age, body mass index, gender, configuration, low-pH, oxygenation index (pO2/FiO2) and underlying disease. Thirty-day mortality was 53% (n = 16) for all comers: 63% (n = 7) died in the vv-group, 75% (n = 6) in the va-group and 27% (n = 3) in the vva-group. Although univariate analysis could not rule out a significant predictor for the outcome, there was a trend visible to decreased mortality in the vva-group when compared to vv- and va-groups (27% vs. 63% vs. 75%; P = 0.057). ECMO provides a survival benefit in patients when considering a predicted mortality rate of 80% in ARDS. The configuration mode appears to impact the outcome as the veno-venoarterial appears to further improve the survival in this subset of patients.

Keywords: Extracorporeal membrane oxygenation; Acute respiratory distress syndrome; Configuration mode

1. Introduction

Extracorporeal membrane oxygenation (ECMO) provides circulatory and respiratory support in patients with acute cardiac and respiratory failure refractory to conventional treatment. Respiratory failure is usually caused by a severe acute respiratory distress syndrome (ARDS) due to different lung pathologies, such as pneumonia, sepsis, cystic fibrosis, chronic obstructive lung disease, lung graft failure, or due to trauma.

Patients with respiratory-failure usually have a predicted mortality above 80% [1]. The Extracorporeal Life Support Organisation (ELSO; http://www.elso.med.umich.edu/) suggests that ECMO is indicated when the mortality risk reaches 80% which is given at a PaO2/FiO2 < 80 on FiO2 > 90% and a Murray score of 3–4. Many centers define slow and fast entry criteria for instituting an ECMO [2] with a regular re-evaluation of predefined parameters.

To date, the venovenous (vv) ECMO is the most commonly applied mode in patients with ARDS. However, if hemodynamic compromise occurs or oxygenation is not sufficient, an upgrade to venoarterial (va) or a veno-venoarterial (vva) ECMO might be necessary [3].

In this study we reviewed our experience in patients who received ECMO for ARDS with a specific focus on the different modes of cannulation.

2. Patients and methods

From 2006 to 2008, 30 patients received ECMO for severe ARDS at our institution. The ECMO was implanted at the intensive care unit (ICU). Seventeen patients developed ARDS due to direct lung injury: eight patients suffered from pneumonia, four developed graft failure after lung transplantation and five had primary lung disease (two patients with idiopathic pulmonary fibrosis, two with cystic fibrosis, one with interstitial pneumopathy due to radiation). Indirect lung injuries included posttraumatic (n = 2) and postoperative ARDS (n = 7) (one graft replacement of the descending aorta, one CABG, two aortic valve surgeries, one renovisceral rebranching, one resection of an oesophago-tracheal fistula, one liver transplantation) as well as
ARDS due to sepsis (n = 2) and near drowning (n = 1). In one patient, the ECMO was implanted preoperatively before resection of a carcinoma with tracheal necrosis. The baseline characteristics, underlying diseases, configuration modes and upgrades are summarized in Tables 1–3.

Before considering patients for ECMO, conventional treatment for ARDS was applied including lung recruitment maneuvers, prone positioning and NO inhalation to minimize the intrapulmonary shunt. Patients who presented with a PaO₂/FiO₂ < 150 or a severe hypercapnia with a pH < 7 despite conventional treatment were evaluated for ECMO.

Patients were divided into three groups according to their configuration mode: initially, in 18 patients, ECMO was applied in venovenous fashion (n = 18), nine were run in the venoarterial mode (n = 9), and three were started in veno-venoarterial fashion (n = 3) (Fig. 1). The initial configuration was chosen by the surgeon and intensivist on duty. The configuration was then changed in 11 cases: eight patients were upgraded from veno-venous (n = 5) or venoarterial (n = 3) to veno-venoarterial ECMO and two patients were switched from vv to va (Tables 2 and 3) resulting in the following groups: venovenous (vv; group A; n = 11), venoarterial (va; group B; n = 8) and veno-venoarterial (vva; group C; n = 11).

The most frequent cause for change of configuration was poor oxygenation (n = 8), but also hemodynamic compromise (n = 1) and insufficient venous drainage (n = 2). A change of the cannulation site was either necessary for modification of the ECMO configuration or due to hypoperfusion (n = 1), hypoperfusion (n = 1), insufficient venous drainage (n = 2) and high pressure in the ECMO circuit (n = 1) (Table 3). A venoarterial ECMO was considered initially when the mean pulmonary arterial pressure was > 35 mmHg.

For venous cannulation, a percutaneous access was preferred via the common femoral veins and/or the internal jugular vein. If sufficient drainage was not achieved, a three-cannula technique was applied, draining blood both from the internal jugular and the femoral vein and returning oxygenated blood via a cannula in the contralateral femoral vein which was positioned in the right atrium. Another approach was to use both common femoral veins for drainage and the internal jugular vein for arterial return. For arterial cannulation, the subclavian or common femoral artery was used. An 8 mm graft (Vascutek, Inchin- nan, Renfrewshire, UK) was anastomosed end-to-side to the artery, and a 20F cannula (FemFlex II; Edwards Lifesience, Irvine, CA, USA) was inserted in the graft.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 30)</th>
<th>Survivors (n = 14)</th>
<th>Non-survivors (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Demographics</strong></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>47.2 ± 18.4</td>
<td>46.1 ± 17</td>
<td>48.1 ± 19.6</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>60.0/40.0</td>
<td>45.3/56.5</td>
<td>68.8/30.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 ± 10.5</td>
<td>169.2 ± 9.4</td>
<td>168.9 ± 11.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 3.9</td>
<td>23.6 ± 3.3</td>
<td>23.6 ± 4.5</td>
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<tr>
<td><strong>B. Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COPD</td>
<td>2 (6.7)</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>6 (20.0)</td>
<td>1 (7.1)</td>
<td>5 (31.3)</td>
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<tr>
<td>Valvular heart disease</td>
<td>2 (6.7)</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>5 (16.7)</td>
<td>3 (21.4)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>PAD</td>
<td>1 (3.3)</td>
<td>0</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>8 (26.7)</td>
<td>2 (14.3)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>MI in history</td>
<td>3 (10.0)</td>
<td>0</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>CVI in history</td>
<td>2 (6.7)</td>
<td>1 (7.1)</td>
<td>1 (6.3)</td>
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<tr>
<td><strong>C. Haemodynamics before ECMO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>68 ± 11</td>
<td>69 ± 10</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>100 ± 25</td>
<td>99 ± 22</td>
<td>103 ± 29</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>9.9 ± 2.9</td>
<td>10.3 ± 3.6</td>
<td>9.5 ± 2.1</td>
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<tr>
<td><strong>D. Arterial blood gas before ECMO</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pO₂ (kPa)</td>
<td>8.1 ± 2.9</td>
<td>8.2 ± 2.9</td>
<td>8.2 ± 3.1</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>9.0 ± 3.9</td>
<td>8.7 ± 3.8</td>
<td>8.4 ± 5.0</td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mmHg)</td>
<td>68 ± 31</td>
<td>75 ± 37</td>
<td>75 ± 24</td>
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<tr>
<td>pH</td>
<td>7.19 ± 0.27</td>
<td>7.26 ± 0.09</td>
<td>7.13 ± 0.20</td>
</tr>
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</table>

BMI, body mass index; COPD, chronic obstructive lung disease; PAD, peripheral arterial disease; MI, myocardial infarction; CVI, cerebrovascular insult; MAP, mean arterial pressure; HR, heart rate; Hb, hemoglobin.
The whole system including cannulae was coated with heparin and for priming, 1 l Ringerfundin (B. Braun, Melsungen, Germany) and 5000 IU heparin was used.

Initially, the blood flow was set to 4–6 l/min depending on the patient’s body surface area to achieve a 100–150% of calculated flow. In the vva-setting, the amount of arterial flow directed to the venous and arterial cannula was set such that the best possible oxygenation was achieved, usually at a rate of 2:3 (arterial:venous). The gas flow was set to 4–6 l/min with a FiO2 at 100% and the ventilator was set to a positive end-expiratory pressure (PEEP) < 10 cm H2O, peak inspiratory-pressure < 26 cm H2O, FiO2 < 0.5, and a respiratory rate between 14 and 20. These settings were adjusted with regards to O2-saturation accordingly.

Gas exchange was measured by SaO2, paO2 and paCO2. For anticoagulation, a bolus of 100 IU/kg heparin was given before cannulation. Thereafter, the activated clotting time (ACT) was adjusted between 150 and 180. Coagulation was assessed by ACT, thrombin-time (TT), antithrombin III (AT-III) and platelet count. We also measured lactate dehydrogenase (LDH) and hematocrit (Hct) to indentify hemolysis. Both a low platelet count (< 50,000/μl) and a low Hct (< 30%) were corrected by transfusions. For detection of potential hyperperfusion and compartment syndrome, peripheral-pulses and limb circumferences were measured, and both creatinine kinase (CK) and lactate levels were determined.

The gas flow into the ECMO circuit and the FiO2 on the oxygenator were reduced by steps of 0.5 l/min over a period of 12–24 h, to wean a patient from a venovenous ECMO while carefully measuring the pO2, pCO2 and the pH. Before ECMO explantation, the gas flow with FiO2 35% had to be < 2 l/min while sufficient blood gases were present. For weaning a venoarterial or veno-venoarterial ECMO, blood flow rates were decreased by 0.5 l/min over periods of 12–24 h while monitoring hemodynamic parameters (blood pressure, central venous pressure, pulmonary pressures, cardiac index, SvO2). When a flow of 1.5 l/min over 12 h was reached with stable hemodynamics, explantation was performed.

2.1. Statistical analysis

All data for this retrospective study were prospectively collected. Primary outcome measure was 30-day mortality. Univariate analysis was applied to identify clinical parameters associated with mortality. Discrete variables were compared using Fisher exact test and continuous variables were analyzed using a Mann–Whitney U-test. The survival was analyzed using Kaplan–Meier curves. Statistical significance was assumed when P-value < 0.05.

3. Results

Of the whole cohort, 16 patients died within 30 days after ECMO implantation (53%) of which 15 patients expired while being on ECMO, and one patient seven days after ECMO explantation. In detail, 27% (n = 3) died in the vva-group (group C; n = 11; including three patients from the beginning and eight patients upgraded), 63% (n = 7) died in the vv-group (group A; n = 11) and 75% (n = 6) died in the va-group (group B; n = 8).

Although univariate analysis did not rule out a significant predictor for the outcome [age; P = 0.934/body mass index; P = 0.712/gender; P = 0.457/low pH; P = 0.129/low oxygenation index (pO2/FiO2); P = 0.752/underlying disease; P = 0.685], patients who received a veno-venoarterial ECMO
displayed a decreased mortality when compared to patients on veno-venous or veno-arterial mode (27% vs. 63% vs. 75%; \( P = 0.057 \)). ECMO, extracorporeal membrane oxygenation.

Causes of death were multiorgan-failure (MOF) in 13 patients: six patients due to sepsis, one due DIC, and six due to undefined reasons. The mean time of ECMO was 7.53 ± 7.21 days. The median length of hospital stay was 36.5 days. The median length of ICU stay was 21.5 days.

Bleeding was the most frequent complication (72%) (Table 4). In v-v-ECMO, bleeding occurred in one patient, whereas in an arterial cannulation-site, bleeding was found in seven cases (n = 7). One patient developed a hyperperfusion syndrome while the subclavian artery was cannulated. One patient had a hypoperfusion syndrome of the leg. Both the vena and arteria femoralis were cannulated for va-ECMO. After hypoperfusion was diagnosed an additional cannula for distal perfusion was placed in the femoral artery.

Mean follow-up time was 21.1 months. During the follow-up period three patients died: one due to cardiogenic-shock, one due to acute pulmonary-edema two years after lung transplantation and one due to ischemic brain-injury.

4. Discussion

ARDS is still associated with a high mortality-rate varying from 15 to 72% depending on the study [4]. A decrease of mortality from ARDS, as seen by some authors over the last decade [4, 5], is discussed controversially in the literature [6]. The wide variation of mortality rates which are reported may be due to the fact that patients meeting current American–European Consensus Conference ARDS criteria may have highly variable levels of lung-injury and outcomes [7].

Considering a predicted mortality rate of 80% according to ELSO, our study shows that ECMO therapy in general provides a survival benefit in our patients by reducing the 30-day mortality rate down to 53.3%. These findings are in line with other reports suggesting mortality rates ranging between 46% and 50% [3, 8, 9]. Furthermore, our results demonstrate that the configuration mode of ECMO may have an impact on the outcome as the applied veno-venoarterial mode seems to further improve the survival in this subset of patients.

However, although the mortality in the veno-venoarterial subgroup was found to be much lower than in the total cohort (27% vs. 53.3%), statistical analysis only revealed a trend to a reduction in mortality, which, however, was close to significance. This is, at least, remarkable, taking into account the small numbers of patients. It reflects our positive clinical experience with the veno-venoarterial mode in our study cohort. Since this configuration is currently favored as initial ECMO mode in our center, we will be able to see in the near future if and to which extent it may provide a survival benefit. So far, according to our knowledge, there are no reports in the literature which focus on survival depending on different modes of configuration.

We can only speculate why the veno-venoarterial configuration may provide a survival benefit. With this mode, well-oxygenated blood is provided to the systemic and pulmonary circulation. In the pulmonary circulation, it helps reduce the pulmonary resistance and the existence of intrapulmonary-shunts, which might facilitate pulmonary recovery. In the systemic circulation, it takes care for sufficient oxygen supply to the brain, the coronary circulation and all peripheral organs which might prevent multiorgan dysfunction and adds to hemodynamic stability.

Our statistical analysis did not identify independent predictors of outcome. In contrast, other studies found parameters, such as length of mechanical ventilation, pH-value and \( \text{pao}_{2}/\text{FiO}_{2} \) ratio before ECMO implantation as well as age and gender as predictors for outcome [3, 8]. This might be explained by the different size of cohorts. We have reviewed only 30 patients over a period of three years, while the other studies comprise 100 and 255 patients collected over a period of 6.5 and 15 years.

Although bleeding complications were much more frequent in patients with arterial cannulation, this did not affect 30-day mortality. Other investigators identified significant surgical site bleeding as patient-related complications associated with outcome [3]. The bleeding rate of 27% in our study is comparable to that reported by others [10, 11]. Bleeding was mainly located at the arterial cannulation sites. With increasing experience, however, we have noted a decreasing frequency of such complications over the study period. In any case, the bleeding rate has declined as compared to earlier years [12] since heparin-coated ECMO systems and cannulae require much less anticoagulation.

There are several limitations of this study. The patient cohort was small, heterogeneous and due to its retrospective nature, all established disadvantages apply. No algorithm for choosing an ECMO configuration existed when we started the ECMO program. The choice of ECMO configura-
tion may have been influenced by the preferences of the surgeon and intensive care specialist on duty. As the patients were not randomized, there might be a certain selection bias. The survival is poor as compared to other surgical therapies in medicine. However, increasing experience with this therapy will improve the results and justify the economic costs.

ECMO therapy provides a survival benefit in patients when considering a predicted mortality-rate of 80% in ARDS. The configuration mode of ECMO may impact the outcome as the veno-venoarterial mode appears to further improve the survival in this subset of patients.

References


