Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation

Mario Nosotti, Lorenzo Rosso, Davide Tosi, Alessandro Palleschi, Paolo Mendogni,*
Ilaria Faustina Nataloni, Stefania Crotti and Paolo Tarsia

a Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS ‘Ca Granda’ Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
b Department of Anesthesiology and Intensive Care, Fondazione IRCCS ‘Ca Granda’ Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
c Respiratory Medicine Unit, Fondazione IRCCS ‘Ca Granda’ Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

* Corresponding author. Thoracic Surgery and Lung Transplantation Unit, Fondazione IRCCS ‘Ca Granda’ Ospedale Maggiore Policlinico, University of Milan, Via Francesco Sforza 35, 20122 Milan, Italy. Tel: +39-02-5035513; fax: +39-02-5035587; e-mail: paolo.mendogni@unimi.it (P. Mendogni)

Received 11 July 2012; received in revised form 19 September 2012; accepted 24 September 2012

Abstract

OBJECTIVES: A large number of transplantation centres consider extracorporeal membrane oxygenation as an inappropriate option for bridging critical patients to lung transplantation. Technical improvements such as the introduction of a polymethylpentene membrane, new centrifugal pumps and heparin-coated circuits have led to a safer application of extracorporeal membrane oxygenation, and an increasing number of centres are reporting their positive experiences. The aim of this study was to review our practice in bridging critical candidates to lung transplantation with extracorporeal membrane oxygenation, by comparing patients with invasive mechanical ventilation with patients with spontaneous breathing.

METHODS: The records of candidates for lung transplantation treated with extracorporeal membrane oxygenation have been revised.

RESULTS: From February 2008 to 2012, 11 patients who experienced an abrupt worsening of their respiratory conditions were treated with extracorporeal membrane oxygenation; mean age: 33.9 ± 13.2 years, male/female ratio: 5/6, 6 patients were affected by cystic fibrosis, 2 had chronic rejection after transplantation, 2 had pulmonary fibrosis and 1 had systemic sclerosis. Seven patients were awake, while 4 patients received invasive mechanical ventilation. The sequential organ failure assessment score significantly increased during bridging time and this increase was significantly higher in the intubated patients. All the patients had bilateral lung transplantation. Spontaneously breathing patients showed a tendency to require a shorter duration of invasive mechanical ventilation, intensive care unit stay and hospital stay after transplantation. One-year survival rate was 85.7% in patients with spontaneous breathing vs 50% in patients with invasive mechanical ventilation.

CONCLUSIONS: Extracorporeal membrane oxygenation in spontaneously breathing patients is a feasible, effective and safe bridge to lung transplantation.

Keywords: Bridge • Extracorporeal membrane oxygenation • Lung transplantation

INTRODUCTION

Patients listed for lung transplantation who progress to respiratory failure can be supported with mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO); these patients have traditionally been considered as bad candidates for lung transplantation [1]. Such negative awareness has been confirmed by a recent analysis on United Network of Organ Sharing data that indicates mechanical ventilation and ECMO as strong predictors of an adverse outcome [2]. In addition, the invasive mechanical ventilation (IMV) has well-known deleterious effects on the respiratory system, such as barotrauma, volutrauma and the toxic effect of oxygen [3]. However, a few successful cases of ECMO as a bridge to lung transplantation have been reported over the years [4]; furthermore, we have previously described our early experience with ECMO bridge, underlining the promising efficacy of the procedure in non-sedated patients [5]. Encouraged by the early positive results, we insisted on this direction, and in the present study, we review our case series of patients supported preoperatively by ECMO.

MATERIALS AND METHODS

We performed a retrospective review of patients who have undergone lung transplantation while on ECMO support from February 2008 to 2012. Data were acquired from patient files and the North Italian Transplant programme database.
ECMO was selectively initiated to support patients with advanced respiratory failure despite maximal invasive or non-invasive ventilation treatment. ECMO bridge to lung transplantation was considered in selected cases in which the patient presented an abrupt deterioration of chronic lung disease while on the waiting list for lung transplantation. Occasionally, patients on ECMO support without the recovery of lung function despite adequate treatment, and not previously listed for transplantation, received lung transplantation. Patients with extrapulmonary organ dysfunction or sepsis were excluded from ECMO support. All patients received a systemic anticoagulation through the intravenous administration of heparin in order to maintain a partial thromboplastin time ratio between 1.5 and 1.8. Blood flow was managed to obtain a partial pressure of oxygen >60 mmHg, while gases were administered to maintain pH over 7.35. The shift from venovenous to venoarterial ECMO support was considered in the case of right heart failure. Routine antibiotic prophylaxis was avoided. To analyse the effect of maintaining patients awake during ECMO support, we divided the cohort of patients into two groups according to IMV use.

To describe and quantify organ function during the stay in the intensive care unit (ICU), we chose the sequential organ failure assessment (SOFA), a score system which includes respiratory function, coagulation, liver function, cardiovascular function, central nervous system function and renal function [6].

The statistical analyses were made with the JMP software, SAS Institute Inc. (Cary, NC, USA). Continuous variables are presented as mean and standard deviation, while categorical variables are reported as simple number or percentages. The Kaplan–Meier test was used to estimate survival rates. All reported P-values are two sided and values <0.05 were considered statistically significant.

### RESULTS

During the observation period, 11 patients underwent lung transplantation after ECMO support; indications for lung transplantation were cystic fibrosis (n = 6), pulmonary fibrosis (n = 2), bronchiolitis obliterans syndrome after lung transplantation (n = 2) and lung fibrosis secondary to systemic sclerosis (n = 1). Indication for ECMO support was severe hypercapnia with respiratory acidosis (despite the optimal management of the IMV or non-invasive ventilation) and/or intense hypoxaemia. Four patients received ECMO support during IMV and constituted the ‘IMV–ECMO’ group; 7 patients received ECMO support with light sedation and cycles of non-invasive ventilation, these patients were included in the ‘awake–ECMO’ group. The patient characteristics and outcome data are shown in Table 1. Both groups were comparable in terms of age, body mass index (BMI), pO2/FiO2 ratio, pCO2 and pH immediately before the ECMO implantation. Disease severity evaluated with the SOFA score was similar in both groups before ECMO support. All patients received veno-venous ECMO support through percutaneous access to femoral veins. A shift into veno-arterial ECMO was necessary in 5 patients for the development of right heart failure during transplantation; these patients returned to veno-venous ECMO at the end of the surgical procedure. Patients were supported with ECMO for a median of 12.1 days before lung transplantation; there was no difference between the two groups in the duration of preoperative ECMO. None of the patients could be weaned from extracorporeal support and none of the patients died during the ECMO bridge. Paired t-test revealed a significant increase in the SOFA score between the implantation of ECMO and the assessment done right before transplantation (P = 0.008); such increase was significantly higher in the IMV–ECMO group (P = 0.022).

### Table 1: Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Awake–ECMO group</th>
<th>IMV–ECMO group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>5/6</td>
<td>4/3</td>
<td>1/3</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.9 ± 13.2</td>
<td>33.8 ± 12.6</td>
<td>34.0 ± 16.2</td>
<td>ns</td>
</tr>
<tr>
<td>BMI</td>
<td>20.5 ± 3.7</td>
<td>21.2 ± 4.2</td>
<td>19.0 ± 2.2</td>
<td>ns</td>
</tr>
<tr>
<td>pO2/FiO2 before ECMO</td>
<td>151.0 ± 120.3</td>
<td>167.5 ± 147.8</td>
<td>122.2 ± 52.7</td>
<td>ns</td>
</tr>
<tr>
<td>pCO2 before ECMO</td>
<td>86.8 ± 34.6</td>
<td>75.8 ± 32.8</td>
<td>106.1 ± 32.6</td>
<td>ns</td>
</tr>
<tr>
<td>pH before ECMO</td>
<td>7.23 ± 0.14</td>
<td>7.28 ± 0.13</td>
<td>7.15 ± 0.14</td>
<td>ns</td>
</tr>
<tr>
<td>SOFA before ECMO</td>
<td>4.9 ± 1.4</td>
<td>5.0 ± 1.5</td>
<td>4.7 ± 1.5</td>
<td>ns</td>
</tr>
<tr>
<td>Bridging time (days)</td>
<td>12.1 ± 14.7</td>
<td>12.1 ± 18.3</td>
<td>12.2 ± 7.0</td>
<td>ns</td>
</tr>
<tr>
<td>SOFA before LTx</td>
<td>7.4 ± 2.3</td>
<td>6.2 ± 1.2</td>
<td>9.5 ± 2.6</td>
<td>ns</td>
</tr>
<tr>
<td>LTx double/single</td>
<td>11/0</td>
<td>7/0</td>
<td>4/0</td>
<td></td>
</tr>
<tr>
<td>Operative mortality</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>IMV after LTx (days)</td>
<td>27.1 ± 20.7</td>
<td>18.1 ± 18.1</td>
<td>40.5 ± 18.6</td>
<td>ns</td>
</tr>
<tr>
<td>ECMO after LTx (days)</td>
<td>4.6 ± 4.6</td>
<td>5.3 ± 5.6</td>
<td>3.5 ± 3.1</td>
<td>ns</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>30.2 ± 20.4</td>
<td>21.1 ± 18.8</td>
<td>43.2 ± 16.5</td>
<td>ns</td>
</tr>
<tr>
<td>Haemodialysis after LTx (yes/no)</td>
<td>5/5</td>
<td>2/4</td>
<td>3/1</td>
<td>ns</td>
</tr>
<tr>
<td>PGD 72 h grade 0/1/2/3</td>
<td>1/4/1/4</td>
<td>1/2/0/3</td>
<td>0/2/1/1</td>
<td>ns</td>
</tr>
<tr>
<td>CIP-CIM</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>SOFA 7 day</td>
<td>5.1 ± 4.3</td>
<td>4.1 ± 4.4</td>
<td>6.5 ± 4.5</td>
<td>ns</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>47.6 ± 21.9</td>
<td>38.1 ± 19.1</td>
<td>61.7 ± 19.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; BMI: body mass index; SOFA: sequential organ failure assessment; LTx: lung transplantation; ICU: intensive care unit; PGD: primary graft dysfunction; CIP: critically ill polyneuropathy; CIM: critically ill myopathy.
All patients received double-lung transplantation; 2 patients had grafts treated with ex vivo lung perfusion (1 patient in each group). Mean postoperative ECMO support was 4.6 ± 4.6 days (awake–ECMO group: 5.3 ± 5.6 days; IMV–ECMO group: 3.5 ± 3.1 days). Mean IMV time after lung transplantation was 18.1 ± 18.1 days in the awake–ECMO group vs 40.5 ± 18.6 days in the IMV–ECMO group; the difference, however, was not statistically significant. The mean ICU stay after lung transplantation was 21.1 ± 18.8 days in the awake–ECMO group vs 43.2 ± 16.5 days in the IMV–ECMO group; this difference was also not statistically significant. One of the patients in the awake–ECMO group died 2 h after transplantation from unmanageable diffuse bleeding. Two patients in the awake–ECMO group, as well as 2 patients in the IMV–ECMO group, needed a rethoracotomy for bleeding. The 5 patients with bleeding problems had a bridging time of 19.2 ± 20.0 vs 6.3 ± 4.7 days in the remaining patients, though this difference was not statistically significant.

Temporary postoperative haemodialysis was necessary in 3 patients belonging to the awake–ECMO group vs 3 patients in the IMV group. There were not statistically significant differences between the groups in the haemodialysis rate as well as primary graft dysfunction at 72 h. Critically ill polyneuropathy or myopathy rate was significantly higher in the IMV–ECMO group (100 vs 42.8%, P = 0.04). The SOFA index on the seventh postoperative day and the length of hospital stay were, respectively, 4.1 ± 4.4 and 38.1 ± 19.1 days in the awake–ECMO group vs 6.5 ± 4.5 and 61.7 ± 19.6 days in the IMV–ECMO group; the differences were not statistically significant. One-year survival rate was 85.7% in the awake–ECMO group and 50% in the IMV–ECMO group.

**DISCUSSION**

The patients described in this case series all met the standard criteria for lung transplantation and were listed for this procedure, with exception for the first 2 cases. These 2 patients received ECMO support after unsuccessful maximal IMV: the first patient was in acute respiratory distress associated with an underlying pulmonary fibrosis; the second patient had an abrupt worsening of her respiratory function during the work-up for listing. Both patients faced relevant psychological problems when weaned; particularly the second patient, a young woman with cystic fibrosis, needed several months to accept her new condition. These disappointing experiences led us towards a new approach to ECMO support in patients requiring lung transplantation; among other advantages, we believe that vigilant patients have the possibility to participate to his or her clinical progression. Starting from the third case, our strategy had the intention of keeping patients awake and spontaneously breathing during ECMO implantation as well as during waiting time. Despite this intention, another patient of ours received IMV in a hospital 200 km away from our centre; a few days afterwards our anaesthesiologists implanted the ECMO support and transported the patient to our hospital. Lastly, a patient in whom the ECMO bridge was initiated with spontaneous breathing, needed IMV in order to manage bronchial secretions and muscular exhaustion.

In November 2010, new national policies for emergency lung allocation prevented transplantation in patients not previously listed. Such new criterion makes our case series, with only 2 unlisted patients, different from other similar reports where the number of unlisted patients reaches a higher rate (for example, 40% in the Scandinavian report) [7]. Moreover, the Italian emergency allocation programme criteria included age limit (<50 years of age), BMI limits (18–30), presence of extracorporeal support, time limit (<3 weeks), etc.

Patients in the present series suffered from various respiratory insufficiencies; the main problem was due to an improper gas exchange, prevalently hypercapnia. No patient was affected by primary pulmonary hypertension despite elevated pulmonary pressure and moderate right ventricular insufficiency were common. Two-side veno-venous femoral percutaneous cannulation was the approach planned for each ECMO bridge. All patients were successfully bridged to lung transplantation; among the patients with spontaneous breathing, as previously mentioned, one young lady needed a secondary intubation. This case was critically reviewed and it was concluded that the muscular exhaustion, which led to the secondary intubation, was probably a consequence of the progressively worsening respiratory insufficiency rather than an abrupt deterioration. Such experience was congruent with the Hannover report, which stated that secondary intubation of the awake–ECMO patients is considered a negative prognostic factor; in fact, our patient required long mechanical ventilation after transplantation, which ended in a septic shock several weeks later [8].

To analyse the effectiveness of our strategy in keeping the patients vigilant during ECMO, we divided our case series in two groups according to the delivery of IMV. The SOFA score has been chosen to objectively evaluate the patients’ clinical condition. Before initiating ECMO, the SOFA scores were similar in the two groups, but after ECMO support, just before transplantation, the score significantly increased in the IMV–ECMO group. This result could be a step forward in the process of validating the protective role of spontaneous breathing in patients who have permanently lost their respiratory function and are waiting for lung transplantation with ECMO support. In theory, several items could play a positive role during awake–ECMO, such as spontaneous feeding, physiotherapy as well as interaction with relatives and medical staff. An important factor is the preservation of diaphragm function; in fact, the IMV–ECMO group required a longer duration of IMV after transplantation than awake–ECMO group. Furthermore, the well-known detrimental effects of IMV (barotrauma, pneumothorax, decrease in cardiac output, ventilation-associated pneumonia and ventilator-associated lung injury) can be avoided. An ulcerant aid in maintaining patients awake during extracorporeal support will be the widespread use of the dual lumen catheter (Avalon Laboratories, LLC, Los Angeles, CA, USA), which allows an ‘ambulatory ECMO’ as recently reported [9].

We observed a high incidence of intraoperative as well as postoperative bleeding complications in our case series; our data indicate a tendency to have had a longer ECMO bridging time with patients who experienced bleeding problems. However, there were no complications such as haemoptysis, sepsis or cardiac problems, nor were there complications at cannulation sites or in the lower limbs. All the 11 patients reached transplantation after a median ECMO time of 12.1 days (identical in both groups); this may be regarded as a good result, considering the rate of other well-experienced centres [8]. The 30-day mortality was 9% (1 patient), while 1-year survival was satisfactory, reaching 85.7% in the awake–ECMO group. Patients receiving bilateral retransplantation belonged to the awake–ECMO group; bronchiolitis obliterans syndrome was the cause of retransplantation in both. One patient, a 49-year-old man who underwent single-lung transplantation for pulmonary fibrosis 3 years before, received ECMO support for 12 days; in the postoperative period
therefore, the results and the statistical data must be regarded randomized, retrospective analysis of a small number of patients; which is the only one with a consistent number of patients, is descriptions, as shown in Table 2. The Hannover [8] experience, plantation has been rarely reported and mainly is single-case.

Moreover, one must consider organ shortage, which limits lung support to lung transplantation. We stress the necessity to reserve ECMO bridging time. We stress the necessity to reserve ECMO support to manage patients with sufficient muscular strength who experience sudden impairment of their respiratory function.

The experience with ECMO bridge to lung transplantation is still limited: a comprehensive paper from Vienna listed 88 procedures reported in English literature and 38 from Vienna listed own file in the context of over 3000 lung transplantations performed in 2009 [13]. Some well-experienced centres reported the use of Novalung with excellent results; this pumpless ECMO device has a limited potential to increase oxygenation and to decrease pulmonary hypertension; thus, it is preferred in certain specific situations [14]. Awake-ECMO as a bridge to lung transplantation has been rarely reported and mainly is single-case descriptions, as shown in Table 2. The Hannover [8] experience, which is the only one with a consistent number of patients, is very encouraging, as our own experience seems to be.

This paper has several limitations: it is a single centre, non-randomized, retrospective analysis of a small number of patients; therefore, the results and the statistical data must be regarded with caution. However, considering the shortage of data in literature, our study population cannot be regarded as negligible.

In conclusion, our study emphasizes the use of ECMO in spontaneously breathing patients as a feasible, effective and safe bridge to lung transplantation. Compared with ECMO in intubated patients, the awake strategy seems to help keep patients from rapid clinical deterioration during bridging time and to achieve better postoperative survival. The validation of these preliminary results, as well as the patient selection, require further study involving appropriate institutes.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Maria Martellini, Francesco Caridei and Maria Grazia Vitali for their support.

Conflict of interest: none declared.

REFERENCES

We read with great interest the article by Nosotti et al. [1]. The authors presented their experience with the use of veno-venous extracorporeal membrane oxygenation (ECMO) in 11 patients with severe end-stage lung failure awaiting lung transplantation. Seven patients were awake, while 4 patients required invasive mechanical ventilation. The authors describe significant improvements in the 1-year survival rate in non-sedated patients. In addition, the authors found a tendency to shorter duration of mechanical ventilation, intensive care unit stay and overall in-hospital stay for spontaneous breathing patients on ECMO after lung transplantation.

Although we applaud the efforts of Nosotti et al. and recognize the value of ECMO in non-intubated patients to overcome the drawbacks of long-term mechanical ventilation, we believe that the use of the currently available dual-lumen Avalon Elite cannula (Avalon Laboratories, LLC, Los Angeles, CA, USA) offers many advantages in awake, spontaneously breathing patients and should be the preferred approach for patients with acute respiratory failure, and for those being considered for a bridge-to-lung transplantation [2, 3]. Traditional veno-venous ECMO uses a two-cannula technique that requires bed rest and, in most circumstances, necessitates the patient to remain sedated and mechanically ventilated. The Avalon Elite cannula is the first Food and Drug Administration-approved device for single-site veno-venous ECMO in adults. The catheter is usually inserted into the right jugular vein and has 2 lumens; one lumen drains deoxygenated blood from the superior and inferior vena cava, and the other lumen returns oxygenated blood to the right atrium. Due to its unique design, this single-site cannula avoids recirculation of blood and increases the efficacy of ECMO. Additional advantages include not only the possibility to extubate the patient but also to permit ambulation. By allowing the patient to ambulate and to participate in physical therapy, the risk of ventilator-associated pneumonia and deconditioning is significantly decreased [4].

To further reduce the inconvenience of the cannula for awake patients, Shafii et al. described an alternative site to implant the Avalon Elite cannula [5]. Through the left subclavian vein and under fluoroscopic guidance, the cannula can be securely introduced and positioned. The subclavian access was shown to be more comfortable for patient ambulation and easier for nursing care.

In patients requiring prolonged support and specifically for those bridged to lung transplant, veno-venous ECMO with single site cannulation can be an excellent alternative to current cannulation strategies.

Conflict of interest: none declared

References


eComment. Ambulatory veno-venous extracorporeal membrane oxygenation

Authors: Jamil Hajj-Chahine, Christophe Jayle, Paul Menu and Pierre Corbi
Department of Cardio-Thoracic Surgery, University Hospital of Poitiers, Poitiers, France
doi: 10.1093/icvts/vsv487 © The Author 2012. Published by Oxford University Press on behalf of the European Association for Cardio-Thoracic Surgery. All rights reserved.