Support time-dependent outcome analysis for veno-venous extracorporeal membrane oxygenation

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Abstract

Objective: The majority of patients suffering from pulmonary failure refractory to mechanical ventilation require extracorporeal membrane oxygenation (ECMO) support between 1 and 2 weeks. This study was designed to evaluate differences in outcome depending on ECMO duration.

Methods: A retrospective analysis on n = 127 patients requiring veno-venous (VV) ECMO support at our institution between April 2006 and March 2010 was applied. The patient population was divided into three groups according to the support duration (A: 0–10 days, 75 patients; B: 11–20 days, 32 patients; C: >21 days, (max. 67 days), 19 patients). Statistical comparisons between groups were calculated. Results: Mean age of all patients (♀ = 42 patients; ♂ = 85 patients) was 48 ± 16 years (range 15–78 years). Bilateral pneumonia due to bacterial infection (n = 45 patients) or due to aspiration (n = 19 patients) was the main cause for pulmonary failure, other causes were extrapulmonary sepsis (n = 27 patients), major surgery (n = 17 patients), and severe trauma (n = 12 patients). Mean lung injury score (ILS) according to Murray was 3.4 ± 0.4, and mean sequential organ failure assessment (SOFA) score was 12.6 ± 3.7. Statistical comparisons revealed no significant difference in demographic parameters that allow ECMO to be performed relatively safe. An important technological step forward was the development of long-term oxygenators with a polymethylpentene membrane. These oxygenators are associated with reduced red blood cell and platelet transfusion requirements and improved gas exchange compared to previously available oxygenators [2]. Further improvements in circuit components are centrifugal pumps with low hemolysis rates and tip-to-tip heparin coating of all circuit components, allowing short periods of ECMO support without anticoagulation in clinical situations with high bleeding risks [4]. Today, these technological improvements permit the use of ECMO as a percutaneously introduced paracorporeal lung assist enabling ambulation and physical activity in principle [4]. Second, the results of several recent case series and one randomized controlled trial evaluating the role of ECMO for respiratory failure are promising and indicate a cost-effective survival benefit for patients suffering from acute severe pulmonary failure [5–7]. All this led to a recently increased utilization of ECMO for severe respiratory failure.

Keywords: Extracorporeal membrane oxygenation (ECMO); ARDS; Outcome

1. Introduction

The largest randomized controlled trial of extracorporeal membrane oxygenation (ECMO) for respiratory failure more than 30 years ago reported a survival of less than 10% [1]. However, for a number of reasons it is time to review the role of ECMO. First, there have been major technological improvements in circuit components and management optimization that allow ECMO to be performed relatively...
with better survival rates compared to historic trials above 50%. The importance of pulmonary support by veno-venous (VV) ECMO is also underlined by the remarkable survival rates of almost 80% in patients suffering from an H1N1 infection and severe pulmonary failure [8]. Another rather new application area of ECMO is as bridge to lung transplantation where support intervals of 11–107 consecutive days have been reported [9–11]. However, the experience with long-term extracorporeal pulmonary support remains limited. Due to the lack of evidence and appropriate literature, this study was designed to elucidate long-term support defined as longer than 21 days compared to intermediate and short-term ECMO support.

2. Material and methods

A retrospective analysis on n = 127 patients from the Regensburg ECMO Registry suffering from pulmonary failure requiring VV ECMO support at our institution between April 2006 and March 2010 was applied. Severe lung failure was defined if the partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio remained persistently below 85 mmHg, despite optimized invasive ventilation and/or severe respiratory acidosis could not be controlled by conventional and adjunctive methods, including kinetic therapy, high-frequency oscillatory ventilation, and inhaled vasodilators (e.g., nitric oxide).

2.1. Technique of extracorporeal lung support

The extracorporeal device consisted of a centrifugal pump and a membrane oxygenator (Permanent Life Support System, Maquet Cardiopulmonary AG, Hirrlingen, Germany), which was fully heparin coated. Prior to cannulation, an ultrasonographic inspection of the target vessels was aspired to gain information about the correct anatomic location and to exclude thrombotic occlusion. Cannulae were implanted with Seldinger’s technique by experienced physicians. Venous drainage was usually obtained via the right femoral vein, which was cannulated with a 35–40-cm-long 21- or 23-Fr cannula (Maquet Cardiopulmonary AG). For reinfusion, a short 15–17-Fr cannula (Novalung GmbH, Tälheim, Germany) was used, which was implanted into the right internal jugular vein in most cases. The distance between the tips of both cannulae was set to be more than 15 cm to avoid excessive recirculation of blood. In n = 7 patients with predominant retention of CO₂, a single 21-Fr double lumen cannula was introduced into the right jugular vein (Avalon Laboratories, Rancho Dominguez, CA, USA). Blood flow was generated by a centrifugal pump (Rotaflow Centrifugal Pump, Maquet Cardiopulmonary AG). The membrane oxygenator (PLS QuadroxO₂, Maquet Cardiopulmonary AG) is made of polyvinylidenefluoride. It has a total gas exchange surface of 1.8 m² with a low inherent resistance to blood flow and an incorporated heat exchanger. It is approved for long-term use of 14 days. Heparin was administered to increase the activated partial thromboplastin time (aPTT) to 60 sec.

Platelet aggregation was inhibited with 100 mg day⁻¹ of acetylsalicylic acid, if there was no contraindication. In patients with manifest bleeding, heparin was paused up to several days. Oxygen was used as sweep gas with a flow between a maximum of 12 l min⁻¹ and a minimum of 1 l min⁻¹. The extracorporeal support was started with a blood flow of 2 l min⁻¹ and a sweep gas flow of 3 l min⁻¹. Thereafter, blood flow was adjusted according to the arterial oxygenation, and gas flow according to arterial partial pressure of carbon dioxide and pH level. The circuit was monitored twice daily controlling for its gas transfer capability and the pressure drop across the oxygenator. Blood gas analysis was done with Radiometer 700 (Radiometer, Copenhagen, Denmark) (Fig. 1).

2.2. Patient management under ECMO and weaning from extracorporeal support

After implementation of ECMO, invasiveness of mechanical ventilation was reduced to facilitate lung healing. Preset goals for oxygenation were a PaO2 of 65–75 mmHg and PaCO2 was adjusted to achieve a normal arterial pH level. Accordingly, tidal volume (TV) and minute ventilation (MV) as well as positive end-inspiratory pressure (PEEP) and FiO2 were decreased. Positive end-expiratory pressure (PEEP) was initially not reduced to limit potentially progressive atelectasis due to very low TV. Muscle relaxation was discouraged and spontaneous breathing efforts with ventilatory support allowed. After successful treatment of the underlying disease and improvement of lung function, extracorporeal blood flow rate was stepwise reduced to 1.5 l min⁻¹. Thereafter, gas flow was tapered and finally switched off for 30 min. If arterial blood gases and respiratory parameters remained stable, the ECMO system was removed and finally decannulation was done with manual compression of vessels.

2.3. Data collection and statistical analysis

Data were obtained from the Regensburg ECMO Registry. It includes all relevant clinical data comprising, among others, blood gases, laboratory values, complications, and survival. Data were collected prospectively into the database.

![Overall Outcome](image)

**Fig. 1.** Survival between groups.
Statistical analysis was performed with SPSS 17.0 for Windows (SPSS-Inc, Chicago, IL, USA). Continuous variables were first tested for normal distribution with Q–Q plots. The comparison of normally distributed variables between more than two groups was done with analysis of variance (ANOVA) followed by pairwise post hoc test (Bonferroni). Two groups were compared with Student’s t-test. Non-normally distributed data of more than two groups were compared with the Kruskal–Wallis test, whereas Mann–Whitney’s test was used to analyze differences between two groups. Categorical data were analyzed with the Chi-square test ($n \times k$ tables) or with Fisher’s exact test (2 $\times$ 2 tables). Multivariate logistic regression was used to assess the relation of adverse outcome and potential risk factors. $p$-Values $< 0.05$ were considered statistically significant. Survival was defined as survival to discharge home or to a rehabilitation facility. Mortality was defined as in-hospital mortality.

3. Results

3.1. Demographic data

The observational period was from April 2006 to March 2010. A total of 127 patients ($\bar{\chi} = 42; \bar{\lambda} = 85$, mean age $= 48 \pm 16$ years, range 15–78 years) suffering from severe pulmonary failure refractory to optimized mechanical ventilation with a PaO$_2$/FiO$_2$ $< 85$ mmHg were supported with VV ECMO. All patients treated at our institution were included except for children or adolescents below the age of 15 years. The leading cause for pulmonary failure was pneumonia ($n = 45$ patients), and aspiration caused pulmonary failure in 19 patients. Another major patient group included patients suffering from pulmonary failure as a consequence of extrapulmonary sepsis ($n = 27$ patients). Over the entire patient population, a mean sequential organ failure assessment (SOFA) score of 12.6 $\pm$ 3.7 and a lung injury score (LIS) according to Murray of 3.4 $\pm$ 0.4 were calculated. In 36 patients, nitric oxide (NO) was applied and in 39 patients high-frequency oscillatory ventilation (HFOV) was used to improve gas exchange prior to ECMO and afterward. Renal failure requiring renal replacement therapy was present in 51 patients (40%) before installing ECMO, and another 29 patients (22%) developed renal failure on ECMO support. The median time of mechanical ventilation days prior to installing ECMO was 2 days and varied from $< 24$ h up to 61 days. A heparin-induced thrombocytopenia (HIT) was strongly suspected in 16 patients dispersed in all three groups (group A: 7 patients (9.5%); group B: 4 patients (11.4%), group C: 5 patients (27.7%).

3.2. Gas exchange

VV ECMO support improved gas exchange immediately. The PaO$_2$/FiO$_2$ ratio increased from 80 $\pm$ 42 to 129 $\pm$ 72 mmHg ($p < 0.001$) 2 h after implementation of ECMO. It further increased during the following 46 h to 146 $\pm$ 59 mmHg ($p = 0.01$). The improvement in oxygenation was paralleled by a normalization of the PaCO$_2$, which was corrected 2 h after implementation of ECMO (pre-PaCO$_2$ = 68 $\pm$ 23 mmHg, 2 h PaCO$_2$ = 39 $\pm$ 24 mmHg; $p < 0.001$) and remained at that level with a mean PaCO$_2$ of 38 $\pm$ 24 mmHg after 48 h of ECMO support.

The stabilization of gas-exchange parameters was achieved despite a significant reduction of TVs and plateau airway pressures. The TVs were significantly reduced from 462 $\pm$ 13 ml pre-implantation to 330 $\pm$ 11 ml ($p < 0.001$) within 2 h of support and remained at that level during the following 46 h (TV$_{48}$ h = 308 $\pm$ 12 ml; $p = 0.13$). The plateau airway pressures were reduced from 36 $\pm$ 5.7 to 30 $\pm$ 5.8 cmH$_2$O ($p < 0.001$) within 2 h of support. The plateau pressures could be further decreased during the following 46 h to 28 $\pm$ 5.1 cmH$_2$O ($p < 0.001$) (Table 1).

3.3. Support time-dependent analysis

The majority of the analyzed patient population was supported up to 10 days (group A, $n = 76$ patients, mean support time $6 \pm 2.5$ days). Group B patients were supported between 11 and 20 days ($n = 32$ patients, mean support time $14 \pm 2.2$ days) and group C patients were treated longer than 21 days up to 67 days ($n = 19$ patients, mean support days $= 29 \pm 10$ days). This stratification of the patient population was done arbitrarily.

ANOVA calculated no differences between all three groups with respect to age, body mass index, SOFA, or LIS score (Table 2). The median time of mechanical ventilation prior to installing ECMO was statistically different between groups (group A: 1 days, range 0–36 days; group B: 4 days, range 1–61 days; group C: 5 days, range 1–43 days; $p = 0.03$). The occurrence of renal failure requiring renal replacement therapy prior and on ECMO support was similar between all three groups (Table 2). There was a significant difference in the use of inhaled nitric oxide and high-frequency ventilation between all three groups ($p < 0.001$). Nitric oxide was applied in group A in 10.5% ($n = 8$ patients), in group B in 50% ($n = 18$ patients), and in group C in 52% ($n = 10$ patients). A similar distribution pattern was found in the use of high-frequency oscillatory ventilation (group A: 20%/n = 15 patients; group B 43%/n = 14 patients; group C 55%/n = 10 patients; $p = 0.004$). Eighty-one patients (64%) were success-

Table 1. Leading diagnosis for pulmonary failure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Bilateral pneumonia</th>
<th>Aspiration pneumonia</th>
<th>Extrapulmonary sepsis</th>
<th>s/p Surgery</th>
<th>s/p Chemo</th>
<th>s/p Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>21</td>
<td>11</td>
<td>14</td>
<td>15</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Group B</td>
<td>15</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Group C</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>19</td>
<td>27</td>
<td>17</td>
<td>7</td>
<td>12</td>
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</tbody>
</table>

Abbreviations: Group A: <10 days ECMO support, Group B: >10 < 20 days ECMO support, Group C: >21 days ECMO support, s/p: status post.
fully weaned from ECMO support, and 16 (13%) deceased post weaning from ECMO after a mean period of time of 18 ± 17 days. The period of time was longer in the intermediate group B (n = 3; 24 ± 14 days) and in the long-term group C (n = 2; 45 ± 30 days) compared to group A (n = 11; 10 ± 8 days) (p = 0.06). Overall survival to discharge was 51.2% (n = 65 patients). There was a significant difference in survival between groups with a survival of 59% (n = 45 patients) in group A, a survival of 31% (n = 10 patients) in group B, and a survival of 52% (n = 10 patients) in group C (p = 0.029). There was a significant difference between group A and B (p = 0.005), but not between group A and C (p = 0.39) and C and B (p = 0.17).

### 3.4. Risk-factor calculation

The multivariate logistic regression calculation for risk factors for mortality identified three independent risk factors. Renal failure prior to installing ECMO was associated with an odds ratio (OR) for mortality of 12.1 (OR = 12.1; confidence interval (CI) 3.9–30.0, p < 0.001) and renal failure on ECMO support increased the risk for mortality by 7 times (OR = 7.1, CI 1.9–24.9, p = 0.002). The use of NO increased the risk for mortality by 5.8 times (OR = 5.8, CI 1.9–24.9, p = 0.002).

### 3.5. Complications

The most frequent complication was an oxygenator dysfunction requiring replacement in 29 patients (23%). In group A 2.5% (n = 2 patients), in group B 31% (n = 10 patients) and in group C 89% (n = 17 patients) required at least one oxygenator exchange (p < 0.001). Cannula-related complications (additional cannula, bleeding, thrombosis, and dislocation) occurred in 18 patients (14%). This was more frequent in the short-term group A (see Table 3). A partial thrombosis of the cannulated vessels occurred evidently in 12 patients (9.5%) (group A: n = 8 patients, group B: n = 2 patients, group C: n = 2 patients). One patient (group A) was converted from VV ECMO to VA ECMO due to refractory right ventricular failure. The majority of patients, n = 43 patients (34%), died due to refractory sepsis and multi-organ failure (Table 4).

### 4. Discussion

A population-based estimation in the United States calculated 190 000 cases and 74 000 deaths for acute lung injury each year in the US, which represents an important source of mortality, morbidity, and costs [12]. Projective calculations suggest that with an aging population, there will be a further increase in lung failure in the United States up to 300,000 patients/year in 2030 [13]. The situation in Europe can be assumed to be similar. Furthermore, due to the increasing global travel, viral outbreaks such as the H1N1 flu may further increase the number. Despite various ventilator-focused rescue therapies (e.g., low TV ventilation with high PEEP, HFOV, recruitment maneuvers, prone positioning, and NO) that are used in case of failure of conventional mechanical ventilation, the observed mortality in patients with no improvement in oxygenation in the first 24 h despite optimal therapy is high and varies from 53% to 68% [14,15]. The options for the physician at the intensive care unit (ICU) are limited in this scenario. A recently published review on severe hypoxemic

<table>
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<tr>
<th>Table 3. Complications.</th>
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<tr>
<td><strong>Frequency</strong></td>
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<tr>
<td>Oxygenator thrombosis</td>
</tr>
<tr>
<td>Pumphead Failure</td>
</tr>
<tr>
<td>Cannula Problems</td>
</tr>
<tr>
<td>Bleeding</td>
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<td>Vein thrombosis</td>
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<th>Table 4. Leading causes of death.</th>
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<tr>
<td><strong>Causes of death on support</strong></td>
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<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>MOF</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Lung failure</td>
</tr>
<tr>
<td>Cardiac failure</td>
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<tr>
<td>Unknown</td>
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respiratory failure conducted a literature search about ventilatory strategies in respiratory failure. Each therapy reviewed was reported to improve gas exchange in patients with acute respiratory distress syndrome (ARDS) at least temporarily. However, none of them had an impact on survival, and none of them was reported to be superior [16]. Hence, controversy still exists about the optimal approach, device, and method to support the non-oxygenating failing lung.

Various medical apparatus have been tried to replace or support the lung function. Two comparable devices, still in a preclinical developmental status, are the intravascular oxygenator and the Hattler catheter [17,18]. A simple technique is an extracorporeal CO₂ removal device using a hemofiltration circuit at 300 ml min⁻¹ of blood flow by mounting an oxygenator in series [19]. Another device is the pumpless arterio-venous interventional lung assist (iLA), characterized by a low resistance to blood flow, which is mainly used for CO₂ removal [20,21]. First promising clinical cases have been described in patients with chronic pulmonary hypertension in right ventricular failure, who were successfully bridged over a period of up to 62 days to lung transplant with ILA implanted as an oxygenating shunt between the pulmonary artery and the left atrium [22,23]. The major disadvantage of these devices is the insufficient amount of oxygen transferred due to the inadequate blood flow. Therefore, the upmost-applied apparatus to replace the failing lung is ECMO. The Extracorporeal Life Support Organization now reports over 40 000 ECMO cases in more than 172 centers worldwide since its establishment in 1989, mainly in the neonatal population (www.elso.med.uni-ch.edu). However, ECMO does not treat the cause, but only improves gas transfer. At best, ECMO can avoid further ventilator-associated lung injury while allowing the lung time to rest and heal. To date, it is unclear whether ECMO duration has a negative impact on survival. Only little experience exists with long-time ECMO support. It can be assumed that prolonged ECMO support is necessary in more severely sick patients. Also, a prolonged ECMO run might be associated with more technical and clinical complications. Hence, this study was designed to elucidate long-term veno-venous ECMO support for intractable pulmonary failure with modern devices, and to evaluate a possible impact of ECMO duration on survival. The presented results displayed an overall survival to discharge of 51.2%, which is comparable to recent ECMO trials for respiratory failure [5,24]. Given the fact that a mortality of up to 68% is described in patients suffering from refractory hypoxemic respiratory failure, the observed survival can be considered a success. This is also a slight improvement compared to our first 60 patients published, who had a survival to discharge of 45%. This can be explained by a growing experience with ECMO and better patient selection [7].

The entire patient population presented here was divided into three groups depending on their support time: short-, intermediate, and long-term support. The statistical evaluation revealed no differences in lung injury or general medical status as similar SOFA scores between groups imply. However, the use of nitric oxide and HFOV was more frequent in the intermediate and long-term group. Thus, the seriousness of lung failure can be categorized as more severe in the intermediate and long-term group requiring ventilatory and non-ventilatory strategies to improve gas exchange and finally longer ECMO runs. This fact needs to be taken into consideration comparing the survival results. However, it is also reasonable to hypothesize that the sicker patients deceased earlier in the course and only the less severe survived longer periods. The applied analysis does not clarify this. It is also noteworthy that the outcome after long ECMO runs was comparable to short ECMO runs despite a longer mechanical ventilation period prior to installing ECMO.

ECMO is also increasingly used as a bridge to lung transplantation [4,9]. The outcome of this particular patient population in our presented patient cohort was comparable to existing reports. Out of five patients placed on ECMO with the intention to bridge them to transplantation, four patients were successfully bridged to transplantation (support days: 6, 10, 15, 24, and 67). One out of these four patients could be weaned after 15 days of support before a successful transplantation was performed, and one patient did not survive the post-transplant period.

The regression analysis revealed two risk factors for non-survival. One risk factor was renal failure prior to installing ECMO and on ECMO support. The analysis revealed that the risk for mortality is ~2 times higher when patients are placed on ECMO in renal failure compared to the risk if patients develop a renal failure on ECMO. The second relevant risk factor was the use of NO, which probably mirrors a more severe intractable lung failure with need for additional adjunctive therapeutic options. However, it remains unclear whether NO is a clinical relevant risk factor. It is noteworthy that the duration of ECMO support was not identified as a risk factor for mortality in our patient population (Table 5).

ECMO is a complex technical procedure that is performed on critically ill patients, and, as such, it has a high potential for complications. The incidence of severe adverse events is reported to range between 24% and 55%. This is in accordance with the recorded incidence in the present study (Table 3). Oxygenator failure per se needs to be considered not as a complication but more as consumption. The exchange can be performed in less than 30 s, generally without adverse effects on the patient. Excluding oxygenator failure, the incidence of complications in the current population was 38% overall.

<table>
<thead>
<tr>
<th>Table 5. Transfusion requirements.</th>
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<tr>
<td>A No transfusion A B No transfusion B C No transfusion C p Value</td>
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<tr>
<td><strong>PRBC (Units)</strong></td>
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<td><strong>PLT (Units)</strong></td>
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<td><strong>FFP (Units)</strong></td>
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Abbreviations: PRBC: pure red blood cell units; PLT: platelet units; FFP: fresh frozen plasma units; No transfusion = number and percentage of patients without requiring transfusions
5. Conclusion

VV ECMO in patients suffering from acute lung failure refractory to mechanical ventilation is very successful in rapidly improving gas exchange. Overall, more than 50% of patients survived. Length of ECMO support per se was not associated with a higher mortality. Hence, our group recommends keeping ECMO running as long as needed.

References


Appendix A. Conference discussion

Dr G.A. Patterson (St. Louis, Missouri, USA): I think this is an important paper for surgeons to realize that there has been a dramatic change in the application of ECMO. Your slides show clearly that recent developments have transformed ECMO from a dangerous, cumbersome procedure associated with high mortality to a totally feasible, practical solution for patients with respiratory failure.

I have a couple of comments and two short questions. I think it just doesn’t make sense that long-term ECMO runs would have exactly the same survival as short-term ECMO runs. I think that’s just a matter of your numbers.

Dr Camboni: Yes, and we saw a slight decrease in survival but it didn’t reach statistical significance. That means in other words that long ECMO runs are associated with a decreased survival compared to short time ECMO runs, but the survival is not intolerably worse.

Dr Patterson: Right. Also, I think that your findings, if I understood the manuscript correctly, very much mirror the transplant experience in that patients who are placed on ECMO early following transplant for acute graft dysfunction have a much better survival than patients who get on ECMO late. And I think you have demonstrated here that patients who had a relatively shorter time on a ventilator before ECMO had a better survival than those who were ventilated for a long time, where things were dragged out, before being placed on ECMO.

Dr Camboni: Well, this is true, but, again, the difference did not reach statistical significance.

Dr Patterson: The short-term vent patients weren’t any different from long-term vent patients?

Dr Camboni: Yes.

Dr Patterson: I would also argue that that’s probably a matter of numbers. It’s a terrifyingly feasible, practical ECMO strategy. How do you determine cannula placement so that you maximize drainage? Do you use TEE?

Dr Camboni: We use TEE on a regular basis to avoid recirculation. If we cannot apply TEE, we use transthoracic echocardiography or simply chest radiographs, but TEE is probably the most common approach, yes.

Dr Patterson: And I noticed that in recent years certainly, a number of your patients were transferred from other hospitals to your hospital.

Dr Camboni: Yes.
**Dr Patterson:** Does that represent a large number of the patients, or are most of these patients from your own institution?

**Dr Camboni:** It’s not a large number. It’s a small number. It’s probably less than one-third.

**Dr Patterson:** You have quite a variability in the application of nitric oxide and high-frequency ventilation and strategies, and that probably reflects a lack of a uniform protocol because you’ve got multiple hospitals involved. I don’t know if that’s the case or not.

**Dr Camboni:** That is one reason, and the other reason is that we also have different ICUs and the management is slightly different among these different ICUs, but the ECMO team is the same.