Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is a rescue strategy ensuring gas exchange and protective ventilation in patients with severe acute respiratory distress syndrome (ARDS) who do not respond to conventional therapies.1 Despite the growing interest and widespread use of such technology, there is no adequate trial showing the absolute benefit of ECMO in improving survival and/or quality of life in adult patients with ARDS.2 One reason for the paucity of data in this field is the difficulty of designing a randomised controlled study on ECMO that would have the utmost scientific rigor, in particular on ECMO management.3 There is no evidence on numerous issues regarding ECMO management, such as the ideal settings of the ECMO system and the ventilator, the best site of cannulation, or the choice of cannulae or anticoagulation regimens.4-8 Last, the pathological entities driving ARDS are often different, and therefore it can have a peculiar pathophysiological background.9

Our aim with this retrospective study was to report differences in the management of patients with a primary diagnosis of bacterial pneumonia as the cause of respiratory failure who underwent VV ECMO in five European ECMO centres. The aim of our analysis was to highlight areas of discussion in the management of ECMO patients and therefore create a baseline for future clinical trials aiming to improve treatment.

Methods
We performed a retrospective, multicentre investigation on clinical practice in VV ECMO. Participating centres were the University Medical Center, Regensburg (Germany), the Karolinska University Hospital, Stockholm (Sweden), the Fondazione IRCCS Policlinico San Matteo, Pavia (Italy), the Hôpital Erasme, Université Libre de Bruxelles, Brussels (Belgium) and the San Raffaele Hospital, Milan (Italy). Institutional ethics committee approval was obtained from each centre.

The most recent consecutive 10 cases of adult patients with severe respiratory failure due to primary bacterial pneumonia receiving VV ECMO treatment from January 2014 to February 2016 were reported from each centre. The indication for VV ECMO was met in cases of severe ARDS with a Murray lung injury score of 3 to 4 and a PaO₂/FiO₂ < 80 mmHg, despite optimised conventional therapy, including protective ventilation (low tidal volume, to 6 mL/kg of ideal body weight, and titrated positive end-expiratory pressure [PEEP] to plateau pressure [Pplt] < 30 cmH₂O). A relative indication for VV ECMO was met in the case of a Murray lung injury score of 2 to 3 and a PaO₂/FiO₂ < 150 mmHg, severe respiratory acidosis (pH < 7.25), peak inspiratory pressure > 30 cmH₂O or severe air leaks. All participating centres followed these indications in accordance with the Extracorporeal Life Support Organization (ELSO) guidelines for adult respiratory failure.10 Exclusion criteria were any state of immunosuppression before ECMO therapy, a cause of respiratory failure other than bacterial pneumonia, any other form of extracorporeal life support other than VV ECMO (ie, venoarterial ECMO or low-flow VV ECMO for carbon dioxide removal).

Baseline characteristics and information on ECMO and ventilator settings, anticoagulation and biological values for
patients were collected daily. For all patients, each analysed parameter was reported at nine time points: before ECMO initiation; every day during the first 5 days on the system; on the day before weaning from ECMO; on the last ECMO day; and 1 day after explantation of the system (if this last occurred). Peak pressure (Pmax) was assessed using the plateau pressure if in controlled volume ventilation, or by peak inspiratory pressure if in controlled pressure ventilation. Driving pressure was calculated as Pmax – PEEP.11

Statistical analysis
Continuous data are expressed as means with standard deviations (SDs) unless stated otherwise. Differences between centres were compared by one-way ANOVA. If significant differences between groups were observed, pairwise t tests were used. A two-sided P < 0.05 was considered statistically significant. All analyses were done with SPSS, version 22.0 (IBM).

Results
Forty-eight patients were included in the study. Baseline characteristics of all patients are shown in Table 1. Age and severity of lung failure were comparable among centres as well as the baseline characteristics of patients indicating VV ECMO therapy. ECMO was initiated a median of 1 day (range, 0–37 days) after ICU admission and was used for a mean of 12.8 days (SD, 12.7 days), ranging between 4 and 76 days. Forty-five of 48 patients were weaned from ECMO therapy. Overall ICU mortality was 29%.

Ventilator settings
Ventilator setting results are shown in Figure 1. Median PEEP values before implantation of ECMO showed a small range of differences, varying from 9.7 cmH₂O in some centres to 12.3 cmH₂O in others; however, after implementation of ECMO, this range became wider with different clinical strategies applied. Some centres then followed a strategy of increasing PEEP (from 3.0 to 3.8 cmH₂O), and PEEP was reduced in others (from –0.8 to –3.2 cmH₂O).

All centres used comparable settings for Pmax before the initiation of ECMO, with reported values between 33 and 35 cmH₂O. Reduction of Pmax occurred in all centres after ECMO implementation, but to different extents. Most centres reduced Pmax by an average of 5 cmH₂O, but it was reduced by 11 cmH₂O in one centre. During the first 5 days of ECMO therapy, Pmax was then kept constant in all participating centres. Among centres, the variation in tidal volumes was greater especially from Day 2 of ECMO therapy on (Figure 1D). The reason for this variation is mainly due to the level of sedation of the patients: higher TV possibly indicates spontaneous breathing on pressure support mode rather than controlled ventilation.

Differences occurred during ECMO weaning. The strategy in one centre was to extubate patients and have them on non-invasive ventilation before ECMO was explanted; in another centre, weaning from ECMO was always performed before weaning from the ventilator.

ECMO settings and weaning from the device
There was a significant difference in duration of ECMO runs between centres, ranging from 8.1 days (SD, 7.8 days) in one centre to 19.7 days (SD, 14.3 days) in another centre (P = 0.22).

Data on blood flow and sweep gas flow are shown in Figure 2. Interestingly, the mean blood flow on the day of ECMO initiation was significantly different between centres, ranging from 3.2 L/min (SD, 0.81 L/min) to 4.1 L/min (SD,
0.69 L/min) \( (P = 0.005) \) on the day of ECMO initiation. Thereafter, variations in blood flow settings on ECMO were similar during the first 5 days and differences reflect different approaches to weaning and different courses of the primary disorder (Figure 2).

To provide further details on pump flow and sweep gas management, we calculated the ratio between blood flow on ECMO and sweep gas flow. The mean ratio was 1.0 (SD, 0.46) for all centres, ranging from 0.68 (SD, 0.10) to 1.6 (SD, 0.52) for single centres. For cannulation, the most used strategy was femoral drainage and jugular return mode, but single centres differed in their preference of cannulation strategies. The Milan centre preferred double-lumen jugular cannulae and the Stockholm centre used jugular drainage and femoral return mode.

**Discussion**

This was the first study collecting data on patient management on VV ECMO and it had some unique features. Patients were recruited from five large-volume European centres who shared the same approach, in terms of respiratory and timing indications, to VV ECMO. All patients had the same primary disorder (bacterial pneumonia), which allowed for a reproducible pathophysiological background and clinical course.

Our main findings from this retrospective analysis of clinical management of patients with severe respiratory failure and VV ECMO therapy are that, although the patients were initially in a similar condition, for different European ECMO centres:
• there was great diversity in the management of mechanical ventilation, especially in PEEP settings
• there was no consensus on cannulation or ECMO device settings
• there was no consensus on the ECMO weaning process.

Our aim was to create a baseline for clinical practice in VV ECMO for severe respiratory failure. As different centres often have a great variety of patients with respiratory failure, it is difficult to compare treatment and outcomes between centres. To include comparable patients in this study, inclusion criteria were for patients with primary bacterial pneumonia as the cause of respiratory failure without previous immunosuppression.

Existing evidence on lung-protective ventilation (low tidal volumes, low driving pressure and higher PEEP) in ARDS patients shows that these strategies are established in all participating centres, explaining comparable values for PEEP, Pmax and driving pressure before implementation of VV ECMO. All five centres also adhere to the indication criteria for ECMO support as advised in the ELSO guidelines. Beyond this point, evidence for ventilation strategies is much weaker and leads to greater diversity in patient management. Our study showed that ventilator support is decreased substantially from pre-ECMO levels relating to Pmax and driving pressure, but there is variability in the extent of reduction of Pmax and driving pressure, and opposing strategies in setting PEEP values. These opposing strategies in PEEP settings reflect different pathophysiological ideas, in that the hypothesis of “keeping the lung open” and avoiding interstitial oedema are arguments for higher PEEP, and reduction of right ventricular strain and pulmonary artery pressure are arguments for lowering the PEEP. Which strategy benefits patient outcomes remains to be answered.

There are limited published data on ventilator settings for ECMO patients. A retrospective, international, multicentre study by Schmidt and colleagues showed a positive association of higher PEEP on Day 3 of ECMO therapy, and Bein and colleagues advocated ultraprotective ventilation in combination with extracorporeal life support. There are also reports on spontaneous breathing in patients on VV ECMO. We confirm that ventilation strategies for patients on VV ECMO are at present mainly influenced by institutional opinion, with great variability between centres.

This becomes more complex if we expand the issues of mechanical ventilation to the ECMO setting, with the interplay of the natural lung providing gas exchange and reducing the work of breathing. What is the appropriate blood flow in VV ECMO? Blood flow through the membrane oxygenator is the main determinant of arterial oxygenation and an ECMO flow/cardiac output > 60% has been shown to be associated with adequate blood oxygenation. In clinical practice, cardiac output is not always measured and the native lung gas exchange function, in combination with the ventilation strategy, also plays a crucial role. Our data were consistent in that they showed variability of blood flow on VV ECMO between participating centres, from 3.2 L/min to 4.1 L/min on Day 0. All centres aimed for PaO₂ > 60 mmHg as a primary target of extracorporeal gas exchange. From this perspective, recirculation plays a pivotal role on the efficiency of venous blood oxygenation and greatly depends on cannula positioning. However, cannula positioning is not standardised; there is a huge

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**Figure 2. ECMO settings for patients on VV ECMO from five centres**

ECMO = extracorporeal membrane oxygenation. VV = venovenous. * Presented time points are the first 5 days on the system, the day before weaning from ECMO and the last ECMO day. Values are medians for 10 patients from each centre, except eight patients from Milan.
variety in cannulation with a range of available cannulas, differing cannulation sites and differing flow directions.21,22

The main limitations of our observational study are its retrospective nature, missing data and the small number of patients per centre. It also has to be considered that only expert centres were represented.

Blood flow in the ECMO device during the acute treatment phase (Days 1 to 5) was kept constant in all participating centres, but there was opposing management of weaning from the device. Reducing either sweep gas or blood flow in weaning from the device is a matter of opinion with a lack of evidence. The main argument for reducing pump flow is to reduce shear stress to the blood elements, and the main argument against it focuses on concerns relating to blood clotting.

Conclusions

Our data show the wide spectrum of management currently used in different experienced centres in Europe for patients treated with VV ECMO for respiratory failure. The differences are mainly driven by the lack of evidence in this field. Randomised controlled trials are urgently needed to address these issues, which could improve outcomes in this challenging clinical setting. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of extracorporeal life support in the critically ill.23-26

Competing interests

None declared.

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References


14 Guerin C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. Minerva Anestesiol 2011; 77: 835-45.


