The inflammatory response is central to the pathogenesis of acute respiratory distress syndrome (ARDS), and if severe or unchecked, can lead to endothelial injury, end organ failure and death. Venovenous (VV) extracorporeal membrane oxygenation (ECMO) has been shown to reduce mortality in patients with severe ARDS. Little is known about the associated inflammatory/cytokine response of these patients on the commencement of ECMO, and what impact this has on overall outcomes.

Currently, conflicting data exist on whether ECMO is overall pro- or anti-inflammatory. Exposure of blood to non-endothelialised surfaces has been shown to activate pro-inflammatory cytokines. However, ECMO also restores oxygen supply to hypoxic tissue and enables ultraprotective lung ventilation (eg, tidal volumes of 3–5 mL/kg), which may reduce ongoing ventilator-induced lung injury (VILI) and organ failure.

Understanding the inflammatory response of patients with ARDS who undergo VV ECMO is important. Many current therapeutic strategies are focused on influencing it, such as reducing VILI through lung-protective ventilation. Cytokine removal has been discussed as a therapeutic target to control excessive inflammation. Inflammatory mediators may also enable better prognostication and improved patient selection.

Our primary aim was to examine the immuno-inflammatory response in patients undergoing VV ECMO for severe ARDS.

**Methods**

**Population and setting**

From January 2009 to August 2015, all consecutive adult patients with ARDS who underwent VV ECMO in the University Hospital Regensburg (UKR), were included in the study. The UKR is a tertiary referral hospital in Germany which operates a regional ECMO referral service and performs over 100 ECMO runs per year. Patients were excluded if they had incomplete data on their cytokine levels, or if they did not have ARDS (eg, patients with chronic fibrotic diseases who were being bridged to lung transplantation, or patients who had a near-drowning).

**ABSTRACT**

**Objective:** The immunoinflammatory response is central to the pathogenesis of acute respiratory distress syndrome (ARDS). However, little is known how this is affected by venovenous (VV) extracorporeal membrane oxygenation (ECMO). Our objective was to investigate the factors that influence the inflammatory response of patients with ARDS undergoing VV ECMO, and to analyse the impact of this response on hospital mortality.

**Design and setting:** A prospective observational study of all consecutive patients with severe ARDS who had VV ECMO at a tertiary German ECMO centre from 2009 to 2015. Patients without complete datasets were excluded. Cytokines (interleukin [IL]6, IL8 and tissue necrosis factor [TNFα]) and inflammatory markers (white cell count and C-reactive protein) were assessed before ECMO initiation and on Days 1, 5 and 10, before explantation and at explantation.

**Results:** A total of 262 adult patients undergoing VV ECMO were analysed. Their median Sequential Organ Failure Assessment score was 12, PaO2/FiO2 ratio was 64 mmHg, and overall in-hospital mortality was 34%. Cytokine levels fell quickly within 24 hours and fell further over the first 5 days. Extra-pulmonary ARDS was associated with higher IL6 and IL8 levels compared with pulmonary ARDS. Mechanical ventilation with positive end-expiratory pressure ≥ 15 cmH2O before ECMO was associated with higher IL6, IL8 and TNFα levels. Driving pressures ≥ 19 cmH2O before ECMO were associated with higher IL8 levels. Non-survivors had higher IL6 and IL8 levels for the duration of ECMO.

**Conclusion:** Cytokine levels, on average, fall rapidly after initiation of VV ECMO, which may be related to the reduction of invasiveness of mechanical ventilation. Higher cytokine levels are associated with extra-pulmonary causes of ARDS, more aggressive mechanical ventilation before VV ECMO, and mortality.
ECMO indication and support

ECMO was initiated in patients with severe, potentially reversible respiratory failure, with a PaO₂/FiO₂ ratio of < 80 mmHg on a positive end-expiratory pressure (PEEP) of ≥ 15 cmH₂O, and/or refractory respiratory acidosis (pH < 7.25), despite optimisation of conventional therapy. The ECMO circuit consisted of a centrifugal pump and a coated polymethylpentene oxygenator. Cannulation was performed percutaneously with the Seldinger technique. In most cases, a single-lumen access cannula (21-23Fr) was inserted into the inferior vena cava via the femoral vein, and a short return cannula (15-19Fr) was inserted into the right internal jugular vein. Mechanical ventilation was initiated according to the institution’s standard protocol, and included an open-lung strategy with protective lung settings according to published guidelines. Specifically, for mechanical ventilation during ECMO, tidal volume was rapidly de-escalated to an ultra-low volume (3–5 mL/kg) while the PEEP level was titrated individually to prevent atelectasis. Information on ECMO settings, manufacturers and the institutional protocol for patient management has been described previously and is in the Appendix (online at ccm.org.au/Resources/Publications/Journal).

Data collection

De-identified information relating to pre-ECMO, procedural and post-ECMO characteristics was registered prospectively in the UKR ECMO database. The database contained patient demographic data and information on cardiorespiratory and laboratory parameters, duration of stay and complications. All patients were followed up until in-hospital death (non-survivors) or hospital discharge (survivors). The study was approved by the local ethics committee of the UKR, which waived the requirement for individual patient consent.

Laboratory data

Blood samples were collected daily from all patients. An extended laboratory investigation (including plasma levels of interleukin (IL)6, IL8 and tissue necrosis factor (TNF)α) was done before ECMO initiation, on Days 1, 5 and 10, before explantation and at explantation. The samples were transported to the laboratory immediately after drawing. IL6 levels were measured straight away and IL8 and TNFα levels were frozen and analysed weekly. The IL6 level was analysed using electrochemiluminescence (Cobas e411, Roche Diagnostics), and IL8 and TNFα levels were analysed by chemiluminescence (Immulette 1000, Siemens Healthcare Diagnostics), according to the manufacturer’s specifications.

Study endpoints and definitions

The primary endpoint of our study was to analyse the pattern of immunoinflammatory biomarkers over time in patients with ARDS receiving ECMO. Three subgroup analyses were performed. The first compared the inflammatory response between patients with ARDS of pulmonary origin (primary lung failure) and patients with ARDS of extrapulmonary origin (secondary lung injury). Pulmonary ARDS included bacterial, viral or aspiration pneumonia; extrapulmonary ARDS included lung failure secondary to sepsis or multi-trauma.

The second analysis assessed the association of ventilator settings and cytokine levels. Ventilator settings before ECMO initiation were divided into above-median and below-median values, and the associated interleukin levels for each group were compared over the first 5 days. The third subgroup analysis compared the cytokine patterns between survivors and non-survivors.

Statistical analysis

We show continuous variables as medians with interquartile ranges (IQRs), owing to their non-normal distribution. Categorical data are shown as frequencies with percentages. Differences in plasma concentrations of immunoinflammatory mediators across diagnostic groups were assessed using the χ², Mann–Whitney U or Kruskal–Wallis tests, as appropriate, for categorical, 2-group continuous and multiple-group continuous variables. The cytokine level changes over time were analysed using multilevel models that account for repeated measures on the same individual. For more detailed information see Appendix E1. The repeated-measures analysis was performed using Stata, version 11.2 (StataCorp). All other statistical analyses were performed using SPSS, version 22.0 (SPSS) and SigmaPlot, version 12.0 (Systat).

Results

During the study period, 426 patients underwent VV ECMO for severe respiratory failure. A total of 114 patients with incomplete data and 50 patients requiring ECMO for non-ARDS were excluded, leaving 262 patients in the study population. The median age was 49 years (IQR, 37–60 years), the median SOFA score was 12 (IQR, 8–15), and the median duration of ECMO was 8 days (IQR, 5–14 days). Overall hospital mortality was 90/262 (34%).

Patients with extra-pulmonary ARDS had higher pre-ECMO lactate levels, higher SOFA scores, and longer durations of pre-ECMO mechanical ventilation, compared with patients with pulmonary ARDS (Table 1). Ventilation settings before ECMO initiation were similar between groups. Mortality on ECMO (30% v 18%), hospital duration (37 days [IQR, 18–60 days] v 25 days [IQR, 14–40 days]), and in-hospital mortality (40% v 32%) were higher for extra-pulmonary ARDS. In contrast, patients with extra-pulmonary ARDS had shorter durations of ECMO support (7 days [IQR, 4–10 days] v 10 days [IQR, 6–16 days]).
Table 1. Characteristics of patients with pulmonary v extra-pulmonary ARDS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population (n = 262)</th>
<th>Pulmonary ARDS (n = 159)</th>
<th>Extra-pulmonary ARDS (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>49 (37–60)</td>
<td>51 (39–60)</td>
<td>46 (30–58)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>76 (28%)</td>
<td>51 (32%)</td>
<td>25 (24%)</td>
</tr>
<tr>
<td>Median duration of pre-ECMO ventilation, days (IQR)</td>
<td>1 (1–5)</td>
<td>1 (1–3)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Median pre-ECMO illness severity (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Pao}_2/\text{FiO}_2 ) ratio (mmHg)</td>
<td>64 (52–85)</td>
<td>64 (52–86)</td>
<td>62 (52–82)</td>
</tr>
<tr>
<td>( \text{Paco}_2 ) (mmHg)</td>
<td>64 (53–79)</td>
<td>67 (54–83)</td>
<td>60 (50–71)</td>
</tr>
<tr>
<td>Norepinephrine dosage (mg/h)</td>
<td>1.7 (0.6–3.3)</td>
<td>1.5 (0.5–3.0)</td>
<td>2.0 (1.0–4.0)</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.22 (7.15–7.32)</td>
<td>7.23 (7.15–7.32)</td>
<td>7.21 (7.16–7.32)</td>
</tr>
<tr>
<td>Serum lactate (mmol/L)</td>
<td>2.2 (1.2–4.7)</td>
<td>1.8 (1.1–3.3)</td>
<td>2.9 (1.4–6.7)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>12 (8–15)</td>
<td>11 (8–14)</td>
<td>13 (11–16)</td>
</tr>
<tr>
<td>Median pre-ECMO ventilation parameter (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tidal volume/kg PBW (mL/Kg)</td>
<td>7.0 (6.0–8.2)</td>
<td>7.1 (6.0–8.3)</td>
<td>7.0 (6.1–8.1)</td>
</tr>
<tr>
<td>Driving pressure (cmH(_2)O)</td>
<td>19 (16–22)</td>
<td>20 (16–22)</td>
<td>18 (16–22)</td>
</tr>
<tr>
<td>PEEP (cmH(_2)O)</td>
<td>15 (13–18)</td>
<td>15 (12–18)</td>
<td>15 (13–18)</td>
</tr>
<tr>
<td>Peak Pressure (cmH(_2)O)</td>
<td>35 (30–38)</td>
<td>35 (30–38)</td>
<td>35 (31–40)</td>
</tr>
<tr>
<td>Median hospital support duration, days (IQR)</td>
<td>82 (5–14)</td>
<td>10 (6–16)</td>
<td>7 (4–10)</td>
</tr>
<tr>
<td>ECMO</td>
<td>12 (7–19)</td>
<td>12 (8–22)</td>
<td>11 (7–16)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>26 (16–40)</td>
<td>23 (15–37)</td>
<td>30 (17–42)</td>
</tr>
<tr>
<td>Intensive care</td>
<td>12 (6–16)</td>
<td>28 (18)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Hospital</td>
<td>34 (18)</td>
<td>48 (32)</td>
<td>41 (40)</td>
</tr>
</tbody>
</table>

ARDS = acute respiratory distress syndrome. IQR = interquartile range. ECMO = extracorporeal membrane oxygenation. SOFA = Sequential Organ Failure Assessment score. PBW = predicted body weight. PEEP = positive end-expiratory pressure.

**Figure 1. Cytokine changes according to cause of ARDS**

**Pulmonary and extra-pulmonary ARDS**

Figure 1 shows the trajectories of cytokine levels during the study period. The baseline cytokine level was significantly higher in patients with extra-pulmonary ARDS compared with patients with pulmonary ARDS. Patients with extra-pulmonary ARDS had higher pre-ECMO IL6 levels (1338 pg/mL [IQR, 214–8120 pg/mL] v 349 pg/mL [IQR, 79–3111 pg/mL]; \( P < 0.01 \)), and IL8 levels (154 pg/mL [IQR, 55–223 pg/mL] v 79 pg/mL [IQR, 21–333 pg/mL]; \( P < 0.01 \)).
40 mL [IQR, 36–338 pg/mL]; \( P = 0.02 \). The multilevel model (Table 2) showed that in the extra-pulmonary ARDS group, the geometric mean of the IL6 level was 59.9% higher compared with the pulmonary ARDS group (95% CI, 24.29–78.73%; \( P = 0.01 \)). Similarly, the IL8 level was higher in the extra-pulmonary ARDS group (difference in geometric means, 52.7%; 95% CI, 18.39–72.59%; \( P = 0.01 \)). The IL6 and IL8 levels dropped rapidly after ECMO initiation, particularly over the first 5 days, and then remained stable. TNF\( \alpha \) levels were not different between groups with different causes of ARDS. In contrast, the white cell count (WCC) was only mildly elevated before ECMO, and increased in the extra-pulmonary ARDS group in Days 1–5. C-reactive protein (CRP) also increased from pre-ECMO to Day 1, then fell in the next 10 days.

**Pre-ECMO mechanical ventilation**

The associations between the cytokine levels in three different sub-groups, based on their pre-ECMO ventilation status, are shown in Figure 2. The top three graphs in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pulmonary v non-pulmonary ARDS*</th>
<th>In-hospital survivors v non-survivors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>–59.9% 0.01</td>
<td>–70.4% &lt; 0.01</td>
</tr>
<tr>
<td>IL8</td>
<td>–52.7% 0.01</td>
<td>–76.8% &lt; 0.01</td>
</tr>
<tr>
<td>TNF( \alpha )</td>
<td>–6.7% 0.52</td>
<td>–23.2% 0.02</td>
</tr>
<tr>
<td>WCC</td>
<td>9.77% 0.43</td>
<td>53.6% &lt; 0.01</td>
</tr>
<tr>
<td>CRP</td>
<td>–5.16% 0.70</td>
<td>17.7% 0.25</td>
</tr>
</tbody>
</table>

**Table 2. Estimated associations between type of ARDS, survival status and cytokine levels during the study period, from multilevel models**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pulmonary v non-pulmonary ARDS*</th>
<th>In-hospital survivors v non-survivors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
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<td>–70.4% &lt; 0.01</td>
</tr>
<tr>
<td>IL8</td>
<td>–52.7% 0.01</td>
<td>–76.8% &lt; 0.01</td>
</tr>
<tr>
<td>TNF( \alpha )</td>
<td>–6.7% 0.52</td>
<td>–23.2% 0.02</td>
</tr>
<tr>
<td>WCC</td>
<td>9.77% 0.43</td>
<td>53.6% &lt; 0.01</td>
</tr>
<tr>
<td>CRP</td>
<td>–5.16% 0.70</td>
<td>17.7% 0.25</td>
</tr>
</tbody>
</table>

ARDS = acute respiratory distress syndrome. CI = confidence interval. IL = interleukin. TNF = tumour necrosis factor. WCC = white cell count. CRP = C-reactive protein. * Reference category in the comparison groups. † Per cent change of geometric mean of the cytokine level in the comparison group (pulmonary ARDS or in-hospital survivors) compared with the reference group (non-pulmonary ARDS or non-survivors).

**Figure 2. Cytokine changes according to ventilation settings (PEEP, driving pressure and tidal volume)**

PEEP = positive end-expiratory pressure. IL = interleukin. TNF = tumour necrosis factor. NS = not significant.
Figure 2 compare the trajectory of cytokine levels in the group who received PEEP ≥ 15 cmH₂O with those who received PEEP < 15 cmH₂O. The IL6, IL8 and TNFα levels were higher in patients who had PEEP ≥ 15 cmH₂O (Table 3). The bottom three graphs in Figure 2 show the trajectories of cytokines in patients who had tidal volumes of < 7 mL/kg v those with tidal volumes ≥ 7 mL/kg. The multilevel modelling showed that the level of cytokines did not differ significantly between the two groups over the duration of the study (Table 3). Similarly, the cytokine level variation over time was compared between patients who received mechanical ventilation with driving pressure < 19 cmH₂O and ≥ 19 cmH₂O (Figure 2, middle three graphs). The multilevel modelling showed higher IL8 levels in patients who had a driving pressure ≥ 19 cmH₂O. There was no difference in IL6 or TNFα levels.

In-hospital survival

Figure 3 shows the differences in IL6, IL8 and TNFα levels between in-hospital survivors and non-survivors. ECMO non-survivors had higher pre-ECMO median IL6 levels than survivors (1237 pg/dL [IQR, 148–17 246 pg/dL] v 400 pg/dL [IQR, 89–2850 pg/dL]) and higher median IL8 levels (260 pg/dL [IQR, 76–1786 pg/dL] v 83 pg/dL [IQR, 33–326 pg/dL]). Pre-ECMO median TNFα levels were not different between the groups (31 pg/dL [IQR, 16–60 pg/dL] v 25 pg/dL [IQR, 16–48 pg/dL]). These differences persisted over Day 1. IL8 levels remained higher on Day 5 and at explantation. WCCs were significantly higher in non-survivors than survivors (Table 3). The levels of CRP were not different between survivors and non-survivors. The multilevel modelling showed higher IL6, IL8 and TNFα levels in non-survivors during the study duration. There was a marked reduction in cytokine levels after ECMO initiation in both groups for IL6 and IL8, which lasted until ECMO Day 5. In contrast, for TNFα, a reduction occurred after Day 1.

Discussion

In this large, prospective, cohort study of patients with severe ARDS, we found that cytokine levels decreased rapidly after VV ECMO initiation. We showed that extra-pulmonary ARDS was associated with distinctly higher interleukin levels, and higher PEEP and driving pressures before VV ECMO were associated with higher cytokine levels. High cytokine levels were associated with an increased risk of in-hospital mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-ECMO PEEP ≥ 15 cmH₂O v &lt; 15 cmH₂O*</th>
<th>Pre-ECMO driving pressure ≥ 19 cmH₂O v &lt; 19 cmH₂O*</th>
<th>Pre-ECMO tidal volume &gt; 7 mL/kg v ≤ 7 mL/kg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>150.4 29.64 to 383.51 &lt; 0.01</td>
<td>18.4 –38.18 to 126.73 0.61</td>
<td>–7.43 –51.97 to 78.41 0.82</td>
</tr>
<tr>
<td>IL8</td>
<td>82.5 3.93 to 220.36 0.04</td>
<td>104.0 17.5 to 254.19 0.01</td>
<td>6.1 –39.35 to 85.52 0.84</td>
</tr>
<tr>
<td>TNFα</td>
<td>45.5 17.71 to 79.83 &lt; 0.01</td>
<td>14.9 –6.9 to 41.89 0.2</td>
<td>22.13 –1.14 to 50.87 0.06</td>
</tr>
</tbody>
</table>

ECMO = extracorporeal membrane oxygenation. PEEP = positive end-expiratory pressure. CI = confidence interval. IL = interleukin. TNF = tumour necrosis factor. TV = tidal volume. * Reference category in the comparison groups. † Per cent change of geometric mean of the comparison group cytokine level (PEEP ≥ 15 cmH₂O) compared with the reference group (PEEP < 15 cmH₂O). ‡ Driving pressure was calculated as peak pressure minus the PEEP (in cmH₂O) and grouped according to > 19 cmH₂O and ≤ 19 cmH₂O. § TV per kg of predicted bodyweight (TV/kg PBW) was calculated based on the equation by the ARDSnet trial, and TV/kg PBW of > 7 mL/kg or ≤ 7 mL/kg were compared.

IL = interleukin. TNF = tumour necrosis factor.
Effect of ECMO on cytokine levels

VV ECMO patients constitute a heterogeneous population with a wide range of underlying diseases and comorbidities. Patients with ARDS already have high levels of circulating inflammatory mediators before initiation of ECMO. Previous studies have shown that extracorporeal circuits may be pro-inflammatory in addition to the underlying illness. However, many of these studies have investigated cardiopulmonary bypass (CPB). CPB differs from ECMO in its shorter duration, a concomitant surgical insult and the ischaemia–reperfusion injury.

In a randomised controlled trial of extracorporeal CO₂ removal (ECCO₂R) combined with ultralow tidal volumes (3 mL/kg) v conventional protective ventilation (6 mL/kg), a reduction in IL6 over the first 3 days was observed, and levels were unchanged in the control arm. It is not clear whether this was an effect of the lower tidal volumes, or of the ECCO₂R device. In our study, levels of all cytokines fell rapidly (Figure 1). Several potential mechanisms could account for this. VV ECMO allows for a highly protective lung ventilation and partial lung rest. The improved oxygen delivery may have resulted in a reduction in metabolic and inflammatory activation. The ECMO circuit itself may also absorb cytokines. It seems that the induction of inflammation by ECMO shown in experimental models may be too small to be of clinical relevance, as the levels of cytokines are very high in patients with ARDS. However, these hypotheses need testing in future studies.

 Routinely used markers such as CRP and WCC are slow to react and reflect the extent of acute inflammation poorly. In contrast, IL6 has a central role in leucocyte growth and activation and is a key acute-phase reactant with a rapid onset and a short half-life. It has been shown to be a predictor of severity of ARDS. IL8 is a key neutrophil chemotactic stimulus that recruits neutrophils from the blood to the pulmonary site, and activates neutrophil degranulation. TNFα is pro-inflammatory factor too, and is thought to play an important role in the development of shock, rising after 30–90 minutes and activating other inflammatory mediators.

The differences between levels of cytokines, WCC and CRP show the complexity of the inflammatory response. ARDS is a syndrome that may have several phases, from an initial acute inflammatory exudative phase (Days 1–6), to a subacute proliferative phase (Days 7–14), or fibrotic phase (≥ Day 14). In our population, the median time for initiation of ECMO was 1 day from intubation (IQR, 1–5 days). Concomitant treatments such as antibiotics, haemofiltration or hydrocortisone for septic shock may have influenced the level of cytokines. However, the rapidity and size of the drop suggests these factors cannot fully explain the magnitude of cytokine level decrease.

Effect of cause of ARDS on cytokine levels

The aetiology of ARDS results in distinct patterns of disease. Pulmonary ARDS is more likely to have a local alveolar inflammatory response, but extra-pulmonary ARDS primarily results from vascular endothelial damage mediated through the bloodstream. In our study, the patients with extra-pulmonary ARDS had higher scores for illness severity and higher mortality. They also had significantly higher IL6, IL8 and TNFα levels. In contrast, the CRP level and WCC, markers commonly used in clinical practice to judge severity of disease, were not significantly different from those of patients with pulmonary ARDS. Routine measurement of interleukins, which have a faster and more extensive response to inflammation, may therefore be a useful tool for early recognition of a grave prognosis.

Effect of mechanical ventilation on cytokines: biotrauma

Lung-protective ventilation in ARDS has been shown to reduce the inflammatory response, and to improve overall outcomes. VV ECMO can potentially facilitate an even further reduction of VILI by using ultra-protective settings. We found that PEEP levels ≥ 15 cmH₂O and driving pressures ≥ 19 cmH₂O at baseline were associated with elevated cytokine levels up to Day 5. Driving pressure is directly related to the stiffness of the lung and, therefore, indicates severity of ARDS, as shown in the recent study by Amato and colleagues. However, the association between cytokine levels and mechanical ventilation is complex. It is likely that patients with higher driving pressures also had higher illness severities, so we cannot separate the effects of mechanical ventilation from the underlying illness. Prospective randomised studies are necessary to further explore the direct impact of ventilator settings on cytokines.

Cytokines and mortality

Previous studies have shown that IL6, IL8 and CRP levels are associated with mortality in ARDS, although these results have not been consistent. IL6 level was a predictor of mortality in a heterogeneous population of ECMO patients, but not predictive in another trial. In the current study of VV ECMO patients, non-survivors showed persistently increased levels of IL6, IL8 and TNFα before and during ECMO support (Table 2 and Figure 3). Excessive activation of the inflammatory response has been associated with a risk of progression to multiple organ dysfunction and death. This has formed the basis for potential therapeutic interventions aimed at curbing the inflammatory process. However, these interventions have to be assessed in the light of our results, which showed a massive decrease in cytokines levels within 24 hours by the implementation of ECMO and the associated reduction of aggressiveness of ventilator use alone.
Strengths and limitations
The strengths of our study include the prospective design, the large number of patients with ARDS on VV ECMO and the extensive dataset. The study limitations include its non-randomised study design, which means that causality cannot be proved. A control group of patients without VV ECMO would be desirable. However, it is questionable whether patient datasets with comparable disease severity could be collected, as VV ECMO was initiated in many patients as a rescue procedure.

Conclusions
Our study showed that cytokine levels, on average, fall rapidly after initiation of VV ECMO. The magnitude of this decline makes it likely that this is related to the decrease of aggressiveness of mechanical ventilation, which was the major change in treatment after implementation of VV ECMO. Higher cytokine levels before and during VV ECMO are associated with extra-pulmonary causes of ARDS, a more invasive mechanical ventilation (shown by a higher PEEP and driving pressures), and are associated with an increased risk of death. 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.28-31

Competing interests
None declared.

Acknowledgements
We received a College of Intensive Care Norva Dahlia Foundation Study Grant for a Research Fellowship in Germany. We thank all nurses, perfusionists, physiotherapists and physicians for their outstanding commitment to the care of our critically ill patients.

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