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Autopsy Histopathologic Lung Findings in Patients Treated With Extracorporeal Membrane Oxygenation

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- **Context.**—Extracorporeal membrane oxygenation (ECMO) is increasingly used in the treatment of respiratory and cardiac failure, but data describing lung histopathology in ECMO recipients are limited.

- **Objective.**—To examine pulmonary histopathologic findings in patients who underwent venovenous (VV) ECMO for pulmonary reasons, or venoarterial (VA) ECMO for cardiac indications shortly before death, and to determine if the pulmonary changes provided insights into therapy that may prevent complications and improve outcome.

- **Design.**—We conducted a retrospective study of lung autopsies, from VV and VA ECMO recipients and patients with acute respiratory distress syndrome (ARDS) and non-ECMO treatment, between 2008 and 2020 in Silesia Center for Heart Diseases in Zabrze, Poland.

- **Results.**—Among 83 ECMO patients (42–64 years; male, 57 [68.7%]), the most common histopathologic findings were bronchopneumonia (44 [53.0%]), interstitial edema (40 [48.2%]), diffuse alveolar damage (DAD; 32 [38.6%]), hemorrhagic infarct (28 [33.7%]), and pulmonary hemorrhage (25 [30.1%]). DAD was associated with longer ECMO treatment and longer hospital stay. The use of VV ECMO was a predictor of DAD in patients with ARDS and undergoing ECMO, but it also occurred in 21 of 65 patients (32.3%) in the VA ECMO group, even though VA ECMO was used for heart failure.

- **Conclusions.**—Although DAD was significantly more common in lung autopsies of VV ECMO patients, one-third of VA ECMO patients had histopathologic changes characteristic of ARDS. The presence of DAD in lung autopsies of patients treated with VA ECMO indicates that in these patients, protective lung ventilation should be considered.

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**Outcomes.**

Extracorporeal membrane oxygenation (ECMO) is increasingly used in respiratory and/or cardiac failure to bridge the delay to lung and/or heart transplant, or recovery, as well as in posttransplant primary graft dysfunction. Significant advances in ECMO technology have resulted in better clinical outcomes, but the risk of life-threatening complications is still considerable. Prolonged ECMO therapy is often associated with a systemic inflammatory reaction, with persistent vasoplegia and coagulopathy, which can contribute to multiple organ failure. Changes visible in lung autopsies may be related to both the underlying disease and ECMO treatment. Diffuse alveolar damage (DAD) is considered the pathologic correlate of acute respiratory distress syndrome (ARDS) treated with venovenous (VV) ECMO. However, DAD was also reported in 50% of patients with ARDS who did not receive ECMO treatment, in whom a number of other heterogeneous disorders were also found, including pneumonia. Concurrently, the subgroup of patients with ARDS who also had DAD appeared to be affected by increased mortality. For a correct interpretation of the pulmonary findings in this new era, it is crucial to become familiar with postmortem pathologic pulmonary findings in non-COVID ARDS.

Histopathologic findings in the lungs of patients treated with ECMO are poorly understood. Therefore, our goal was to investigate the histopathologic findings in the lungs of patients undergoing VV or venoarterial (VA) ECMO and to look for clinicopathologic correlations to therapy that might prevent complications and improve outcomes.

**MATERIALS AND METHODS**

**Patients**

Medical records and autopsy files of patients treated at the Clinical Department of Cardioanaesthesia and Intensive Care of the
Silesian Center for Heart Diseases, Zabrze, Poland (2008–2020), who underwent VV ECMO for pulmonary reasons (mainly ARDS) or VA ECMO for cardiac indications shortly before or at the time of death, were queried. During the period covered by the study, 18 autopsies were performed on patients with ARDS treated with VV ECMO and 65 patients treated with VA ECMO for cardiac indications shortly before or at the time of death, were queried. The period covered by the study, 18 autopsies were performed on patients with ARDS treated with VV ECMO and 65 patients treated with VA ECMO for cardiac indications shortly before or at the time of death, were queried. The control group consisted of patients who had died in the intensive care unit with a clinical history of ARDS. Inclusion criteria were the same for both the study group and the control group. Accordingly, an equivalent number of patients with ARDS who had been treated conventionally, without VV ECMO, and underwent autopsy were included in the control group.

The control group was recruited from institutional intensive care unit records (2018–2020) and included patients who had died in the intensive care unit with a clinical history of ARDS, mainly in the control group followed the same process as the study group, with 18 consecutive patients enrolled. Furthermore, the control group was not included to assess whether histopathologic findings in the lungs of patients with respiratory failure treated with VV ECMO may be secondary to ECMO and not related to underlying disease or mechanical ventilation. Medical records were reviewed to define demographic and clinical characteristics of recruited patients and to look for clinico-pathologic correlations. The study was approved by the institutional review board, The Bioethical Committee of the Medical University of Silesia in Katowice (KNW/0022/KB1/65/18), and was completed before the start of the COVID-19 pandemic.

ECMO Management

For VV ECMO, cannulation was performed percutaneously. The venous drainage cannula was inserted into the common femoral vein, while the venous return cannula was inserted into the internal jugular vein. A centrifugal pump integrated with a polymethylpentene hollow fiber oxygenator and heparin-coated tubing was used. The pump speed was adjusted to obtain an oxygen saturation of greater than 92%

For VA ECMO, cannulation was performed in a central or peripheral cannulation. In central cannulation for VA ECMO, venous blood was drained through a cannula placed in the right atrium, and blood oxygenated in the oxygenator was returned through a return (arterial) cannula inserted into the ascending aorta. Peripheral cannulation for VA ECMO entailed drainage of venous blood from the femoral vein and after oxygenation, returned blood through the return (arterial) cannula placed in the femoral artery with the tip in the common iliac artery. As soon as possible, the peripheral configuration was converted to central, or the patient underwent cannulation. A drain was always placed in the peripheral part of the limb. Optimal cannula positioning was verified with a chest x-ray and an ultrasound examination. Unfractionated heparin was administered intravenously (con- tinuous infusion, and boluses, if required) to maintain an activated partial thromboplastin time of 1.5 times normal (50–55 seconds) or 1.5 to 2.0 times normal (55–70 seconds), and to achieve a target activated clotting time of between 160 and 180 seconds and 180 and 220 seconds in VV ECMO and VA ECMO patients, respectively.

Autopsy

According to Polish regulations, autopsy consisted of opening of the thoracic, abdominal, pelvic, and cranial cavities. Only in exceptional cases was autopsy performed without cranial cavity, but always embraced visceral cavities. Sections for histology were collected from each lobe and from areas with gross pathologic changes (eg, infarcts, abscesses). Tissue was fixed in 4% buffered paraformaldehyde for not less than 48 hours, then routinely dehydrated, cleared in xylene, and embedded in paraffin.

Using a standardized preparation approach, hematoxylin-eosin-stained slides and Masson trichrome-stained slides from the lungs of all cases were reviewed by 2 experienced pathologists from our institution, Silesian Center for Heart Diseases in Zabrze, who were blinded to clinical information.

Statistical Analysis

Categorical variables were compared by using the Pearson χ² test or the Fisher exact (2-sided) test. Continuous variables were tested for normality of distribution by the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD, while nonnormally distributed data are given as median and interquartile range (IQR). Comparisons were performed by using the Student unpaired t test or Mann-Whitney U test. Univariate and multivariate logistic regression models were used to identify predictive factors of each histopathologic finding; the odds ratio (OR) with its 95% CI was calculated for each factor. These models included, as the independent variables, age, sex (male versus female), Acute Physiology and Chronic Health Evaluation II score, length of hospital stay, and ECMO duration, as well as ECMO modality (VV versus VA) in ECMO patients or ECMO treatment (VV versus none) in pooled VV ECMO and non-ECMO groups. Quantitative variables were dichotomized by using ECMO group medians as cutoff values. All statistical analyses were conducted with SPSS 22.0 (IBM, New York). P values <.05 were considered statistically significant.

RESULTS

Characteristics of the Studied Groups

We identified 114 patients treated with ECMO. Clinical details and histologic material of the lungs were available for 83 patients (57 men, 68.7%) with a median age of 57 years (range, 42–64 years) at the time of death. VA ECMO and VV ECMO were used for 65 (78.3%) and 18 (21.7%) patients, respectively. The major indications for VA ECMO in the 65 patients were dilated/hypertrophic cardiomyopathy (n = 18, 28%), acute coronary syndrome (n = 11; 17%), use after heart transplant (n = 9; 14%), use after cardiotomy/valvular heart disease (n = 9; 14%), use after cardiotomy/coronary artery bypass grafting (n = 6; 9%), pulmonary thromboembolism (n = 5; 8%), myocarditis (n = 5; 8%), and others (n = 2; 3%).

The major indications for VV ECMO in the group of 18 patients were ARDS associated with bronchopneumonia, septic shock, and influenza A (H1N1) (n = 14; 78%), and after lung transplant for pulmonary fibrosis (n = 4; 22%).

The control group consisted of 18 patients (9 men, 50%) with a median age of 70.5 years (range, 60–73 years) who had died of ARDS associated with bronchopneumonia and were not treated with ECMO (non-ECMO). Demographic and clinical characteristics are presented in Table 1. Median duration of ECMO treatment was 6 days (range, <1–38 days; IQR, 2–10 days). In ECMO patients, median length of hospital stay was 14 days (range, <1–101 days; IQR, 7–28 days).

Histopathologic Findings in Patients Treated With ECMO

Bronchopneumonia, interstitial edema, and DAD were most commonly observed and occurred in 44 (53.0%), 40 (48.2%), and 32 (38.6%) ECMO patients (n = 83), respectively. These findings were followed by hemorrhagic infarction with recent and “recanalization” thromboembolism (28 [33.7%]) and pulmonary hemorrhage (25 [30.1%]). DAD was more frequent in VV ECMO than in VA ECMO patients (P = .03). Acute bronchopneumonia was more prevalent in VV ECMO than in the non-ECMO patients (P = .04), and the opposite was true for interstitial edema. Results of histopathologic examination of lungs from patients who had received VV and VA ECMO are summarized in Figure 1, A, while results of lungs from patients who had received VV ECMO and non-ECMO group are summarized in Figure 1, B.
Clinicopathologic Correlations in ECMO Patients

Association of histopathologic findings of autopsied lungs with clinical parameters in patients treated with ECMO are shown in Supplemental Table 1 (see the supplemental digital content containing 3 tables). Acute bronchopneumonia and the presence of septal fibrosis were related to 100% and 107% prolongation of hospital stay (median [IQR]: 18.0 [10.0–31.75] versus 9.0 [5.0–19.0] days, P = .04) and 28 [10.0–40.0] versus 13.5 [6.0–21.75] days, P = .03), respectively. Intestinal edema was associated with younger age (median [IQR]: 52.0 [37.5–60.75] versus 61.0 [51.0–65.0] years, P = .02). DAD with the formation of hyaline membranes was more frequent in VV ECMO patients than in VA ECMO patients (61.1% versus 32.2%, P = .03). In addition, median ECMO duration was 112% longer (8.5 [IQR, 2.5–14.75] versus 4 [IQR, 2.0–9.0] days, P = .03) and median hospital stay was prolonged by 68% (18.5 [IQR, 10.5–32.75] versus 11.0 [IQR, 5.0–19.0] days, P = .01) in comparison to patients without DAD. Pulmonary hemorrhage was 2-fold more prevalent in the female sex (46.2% versus 22.8%, P = .03) and was related to a 58% shorter ECMO duration (median [IQR]: 3.0 [1.5–8.0] versus 7.0 [3–12.5] days, P = .03) (Table 2).

Logistic regression revealed predictors for certain histologic findings (Supplemental Table 2). Acute bronchopneumonia, in both univariate and multivariate analysis, was inversely related to age 57 years or older (OR, 0.34; 95% CI, 0.14–0.84; adjusted OR, 0.33; 95% CI, 0.12–0.89), whereas length of hospital stay of 14 days or longer implied heightened risk (OR, 2.52; 95% CI, 1.04–6.19; adjusted OR, 4.95; 95% CI, 1.47–16). In multivariate analysis, VV-ECMO was also a risk factor for acute bronchopneumonia (adjusted OR, 4.07; 95% CI, 1.10–15.07). Intestinal edema was inversely associated with age 57 years or older (OR, 0.29; 95% CI, 0.12–0.72; adjusted OR, 0.23; 95% CI, 0.09–0.62). DAD with hyaline membrane formation was related to VV ECMO (OR, 3.29; 95% CI, 1.12–9.70), ECMO duration of 6 days or longer (OR, 2.90; 95% CI, 1.44–7.35), and length of hospital stay of 14 days or longer (OR, 2.90; 95% CI, 1.14–7.35), in univariate analysis. However, in multivariate analysis, only VV ECMO remained a significant predictor (adjusted OR, 3.61; 95% CI, 1.11–11.77). Male sex implied lower risk of pulmonary hemorrhage (OR, 0.34; 95% CI, 0.13–0.93; adjusted OR, 0.32; 95% CI, 0.11–0.92).

Comparison of Patients Treated for Respiratory Failure—With VV ECMO and Conventional Methods

Prevalence of acute bronchopneumonia was significantly higher (P = .04) in the VV ECMO patients than the non-ECMO group, and the opposite was true for interstitial edema (P = .04). Frequency of DAD, lung abscesses, and hemorrhagic infarct with recent and recanalizing thromboemboli, pulmonary hemorrhage, and septal and paraseptal fibrosis was not statistically different between the 2 groups (Figure 1, B). Representative photomicrographs are shown in Figure 2, A through D. Logistic regression modeling was applied to combined groups of VV ECMO and non-ECMO patients to assess whether ECMO treatment is a predictor of lung histopathologic findings in patients with respiratory failure (Supplemental Table 3).

Univariate analysis showed that ECMO treatment was associated with decreased risk of interstitial edema (OR, 0.25; 95% CI, 0.06–0.99) and increased risk of acute bronchopneumonia (OR, 4.08; 95% CI, 1.01–16.58); the former was statistically significant in multivariate analysis (adjusted OR, 0.13; 95% CI, 0.02–0.84). Longer hospitalization increased the risk of acute bronchopneumonia in both univariate (OR, 13.00; 95% CI, 2.27–74.31) and multivariate (adjusted OR, 13.59; 95% CI, 2.08–88.77) analysis. Univariate analysis revealed that age 57 years or older was inversely associated with pulmonary hemorrhage (OR, 0.21; 95% CI, 0.04–0.97), but this effect was not confirmed by multivariate analysis. Hemorrhagic infarct with recent and recanalizing thromboemboli was more frequent in women than in men. This effect was confirmed by both univariate (OR, 0.16; 95% CI, 0.03–0.98) and multivariate (adjusted OR, 0.13; 95% CI, 0.02–0.98) analysis.

DISCUSSION

The main objective of the study was to examine pulmonary histopathologic findings in patients who underwent VV ECMO for pulmonary reasons or VA ECMO for cardiac indications shortly before death. In addition, the study aimed to investigate whether autopsy and histopathologic studies of the lungs of patients who underwent ECMO can provide insights into therapies that might improve patient outcomes.

Lungs from 83 patients autopsied between 2008 and 2020, before the COVID-19 pandemic, who had undergone VV or VA ECMO treatment shortly before or at the time of death, were analyzed. The most common histomorphologic findings were acute bronchopneumonia, intestinal edema, and diffuse DAD, which occurred in 44 (53.0%), 40 (48.2%), and 32 (38.6%) of the 83 patients, respectively. In addition, one-third of patients (28 [33.7%]), were diagnosed with pulmonary hemorrhage and hemorrhagic infarct with recently formed and recanalizing thromboemboli. Also, fibrosis of interlobular partitions and lung abscesses were noted in

Table 1. Demographic and Clinical Characteristics of Study Groupsa

<table>
<thead>
<tr>
<th></th>
<th>ECMO (n = 83)</th>
<th>VA ECMO (n = 65)</th>
<th>VV ECMO (n = 18)</th>
<th>Non-ECMO (n = 18)</th>
<th>VA Versus VV ECMO P Value</th>
<th>VV ECMO Versus Non-ECMO P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>26 (31.3)</td>
<td>20 (30.8)</td>
<td>6 (33.3)</td>
<td>9 (50.0)</td>
<td>.84</td>
<td>.31</td>
</tr>
<tr>
<td>Age, y</td>
<td>57 (42–64)</td>
<td>57.0 (41.5–62.5)</td>
<td>55.5 (42–67)</td>
<td>70.5 (60–73)</td>
<td>.65</td>
<td>.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80 (72–93)</td>
<td>80.0 (72–97)</td>
<td>77 (66–86)</td>
<td>82.5 (75–87)</td>
<td>.14</td>
<td>.01</td>
</tr>
<tr>
<td>ECMO duration, d</td>
<td>6 (2–10)</td>
<td>5 (2–9.5)</td>
<td>9 (3–16)</td>
<td>-</td>
<td>.17</td>
<td>-</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td>14 (7–28)</td>
<td>14 (6.5–25.5)</td>
<td>14.5 (7–32)</td>
<td>10 (2–21.75)</td>
<td>.74</td>
<td>.10</td>
</tr>
<tr>
<td>APACHE II</td>
<td>26 (20–30)</td>
<td>27 (20–32)</td>
<td>25 (20–29)</td>
<td>25.5 (22–30)</td>
<td>.60</td>
<td>.60</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

a Values are No. (%) for categorical variables and medians (interquartile ranges; IQR) for quantitative variables. Bold value indicates significance (P < .05), otherwise statistically nonsignificant (P ≥ .05).

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Autopsy After Extracorporeal Membrane Oxygenation—Trejnowska et al 3
15 patients (18.1%). Some of these histopathologic findings may have been due to underlying disease, but ECMO could have caused others. Autopsy remains an important tool for analyzing disease processes that lead to patient death, though autopsy rates have declined globally in the past few decades.16–20 As a result, very few studies have reported ECMO-related histopathologic findings and mainly include pediatric patients. Chou et al21 reviewed autopsied lungs of 23 pediatric patients (22 infants and a 2-year-old child) who had undergone ECMO. In contrast to the current study, the most common findings during the first few days of ECMO were interstitial and intra-alveolar hemorrhage, with hyaline membrane formation found in more than half of all autopsies.21 Importantly, DAD with hyaline membrane formation occurred in almost all VV ECMO patients in the current study, who, similar to a study by Chou et al,21 had an underlying lung disease that necessitated ECMO. Furthermore, Chou et al21 described parenchymal calcifications, which were not found in ECMO-treated patients in our study. This discrepancy may be related to the difference in age between the study populations. In a similar study, Bond et al22 described 8 cases (neonates: n = 4, infants: n = 3, child: n = 1) of open lung biopsy during ECMO and observed DAD and/or interstitial fibrosis in only 25% of patients. However, the smaller number of patients and different age range likely account for the differences in the results. Studies by Pratt et al,23 Chou et al,21 and Bond et al22 were performed between the 1970s and 1990s, during a different

Figure 1. A, Main histopathologic findings of autopsy lungs in patients treated with VV and VA ECMO. B, Main histopathologic findings of autopsy lungs in patients treated with VV ECMO and non-ECMO group. Values are No. (%). The χ² test or Fisher exact test was performed in all the analyses (2-sided P value). P values <.05 are significant, otherwise statistically nonsignificant (P ≥ .05). Abbreviations: ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.
epoch of ECMO technology than the current study (2008–2020). Indeed, the last 20 years have brought outstanding technological advancements and new materials for extracorporeal circuit production. Significant changes also took place in overall ECMO practice patterns, including anticoagulation strategies and monitoring.24,25

The only, and so far the largest, autopsy study of lungs from patients treated with ECMO shortly before death was published by Lee et al.26 Compared with our results, hemorrhagic changes were twice as common and pulmonary thromboembolic disease, with or without pulmonary infarct, was also more frequent.26 Similar to our study, the most common histopathologic changes were acute lung injuries, such as acute bronchopneumonia, interstitial edema, and DAD with hyaline membrane formation. Furthermore, the latter was also associated with longer ECMO durations.

Differences between the results obtained in the current study and the study by Lee et al26 may have arisen for several reasons. In both studies, most patients underwent VA ECMO, but patients treated with VV ECMO constituted only 10.5% of the ECMO group analyzed by Lee et al26 (5.3% of patients underwent both VA and VV ECMO). Also, Lee et al26 compared patients with VA ECMO to patients who were not treated with ECMO but were hospitalized for cardiac reasons. Meanwhile, the current study looked for differences between patients with respiratory failure who were treated with or without ECMO. Furthermore, a more homogeneous group of patients was analyzed in the current study (age range, 38–64 years), whereas Lee et al26 also reported on children (age range, 3 days–77 years). The difference between patient age in the current study and that of Lee et al26 may account for the difference in the incidence of vascular and parenchymal calcification between the 2 studies. In the study by Lee et al26 similar to the study by Chou et al,23 calcifications were more commonly identified in the infant group than the noninfant group. Indeed, 19 infants (25.0%) and 6 noninfants (7.9%) in the study by Lee et al26 showed vascular and parenchymal calcifications, respectively. The reasons for this discrepancy are unclear, and the clinical significance of calcifications is currently unknown.21,27

The study by Lee et al26 was concluded before the current study (2015 versus 2020), which may explain the higher rates of hemorrhagic pulmonary infarcts and higher incidence of pulmonary hemorrhage in their patients. Indeed, the most common adverse events of ECMO published in the literature and in Extracorporeal Life Support Organization (ELSO) annual reports until 2016 were bleeding and thrombosis as hematologic consequences of maintaining an ECMO circuit.4,27,28 In fact, 75% of our ECMO patients (78% of VV ECMO recipients) were treated between 2016 and 2020, when heparinization was lower (activated partial thromboplastin time no longer than 1.5 × normal29) than in the past, which was enabled by improved extracorporeal circuit biocompatibility.24,25 In the ELSO ECMO report on complications in adults treated for respiratory reasons from 2016 to 2020, pulmonary hemorrhage occurred in 3.4% of patients and was less common than the requirement for renal replacement therapy (26.9%), high creatinine levels (11%), and surgical site bleeding (13.7%).29

The high incidence of acute bronchopneumonia in the current study may be due to the larger subset of patients initially receiving ECMO for pulmonary reasons. Acute bronchopneumonia occurred in 44 of the 83 ECMO patients (53%) and 13 of the 18 VV ECMO recipients (72.2%), much higher than the 25% of patients treated with ECMO for cardiac reasons by Lee et al26. These findings are in line with the results of a large-scale meta-analysis in 2013 that reported bacterial pneumonia in 33% of patients treated with ECMO.30

In our study, we analyzed the lung autopsy results of patients treated with VV ECMO for pulmonary reasons before the COVID-19 pandemic. Thus, we compared the lung autopsy findings of 18 patients treated with VV ECMO to 18 patients treated for respiratory failure who did not receive ECMO. This group of 18 patients still represents the largest published pulmonary autopsy study of patients after VV ECMO.31 Lee et al32 and Kida et al33 reported on 16 and 9 patients, respectively.

The aim of the study was also to determine whether differences in lung histopathology between patients diagnosed with ARDS or severe pneumonia are related to VV ECMO therapy. In this regard, interstitial edema was less common in VV ECMO–treated patients than those treated conventionally, and acute bronchopneumonia was more frequent in the VV ECMO group. Additionally, there were no significant differences in DAD with hyaline membrane formation in patients treated with VV ECMO compared to the non-ECMO control group. These findings may be explained by the fact that VV ECMO and non-ECMO patients had an underlying lung disease—ARDS—and DAD, as the most common histologic pattern identified in patients with

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### Table 2. Main Histopathologic Findings of Autopsied Lungs in Patients Treated With Extracorporeal Membrane Oxygenation (ECMO) and Non-ECMO Group

<table>
<thead>
<tr>
<th>Histopathologic Findings</th>
<th>ECMO (n = 83)</th>
<th>VA ECMO (n = 65)</th>
<th>VV ECMO (n = 18)</th>
<th>Non-ECMO (n = 18)</th>
<th>VA Versus VV ECMO P Values</th>
<th>VV ECMO Versus Non-ECMO P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lung injury</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Acute bronchopneumonia</td>
<td>44 (53.0)</td>
<td>31 (47.7)</td>
<td>13 (72.2)</td>
<td>7 (38.9)</td>
<td>.06</td>
<td>.04</td>
</tr>
<tr>
<td>Intestinal edema</td>
<td>40 (48.2)</td>
<td>33 (50.8)</td>
<td>7 (38.9)</td>
<td>13 (72.2)</td>
<td>.37</td>
<td>.04</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>32 (38.6)</td>
<td>21 (32.3)</td>
<td>11 (61.1)</td>
<td>10 (55.6)</td>
<td>.03</td>
<td>.73</td>
</tr>
<tr>
<td>Lung abscesses</td>
<td>13 (15.7)</td>
<td>9 (13.8)</td>
<td>4 (22.2)</td>
<td>5 (27.8)</td>
<td>.46</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hemorrhagic infarct with recent and recanalizing thromboemboli</td>
<td>28 (33.7)</td>
<td>23 (35.4)</td>
<td>5 (27.8)</td>
<td>3 (16.7)</td>
<td>.55</td>
<td>.69</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>25 (30.1)</td>
<td>18 (27.7)</td>
<td>7 (38.9)</td>
<td>4 (22.2)</td>
<td>.36</td>
<td>.28</td>
</tr>
<tr>
<td>Fibrosis of interlobular partitions</td>
<td>15 (18.1)</td>
<td>10 (15.4)</td>
<td>5 (27.8)</td>
<td>6 (33.3)</td>
<td>.30</td>
<td>.72</td>
</tr>
</tbody>
</table>

Abbreviations: VA, venoarterial; VV, venovenous.

* Values are No. (%). The χ² test or Fisher exact test was performed in all the analyses (2-sided P value). Bold values indicate significance (P < .05).
ARDS, was present in both.\textsuperscript{7,31} However, even though DAD was more frequent in the VV ECMO group than in the VA ECMO group, it was present in 21 patients (32%) despite VA ECMO being used for heart failure.

Therefore, since the variations in the ventilation and fluid management techniques used represent newer management methods that have improved outcomes in patients with ARDS and, consequently, DAD,\textsuperscript{31} this change in ventilation might be also considered in patients undergoing VA ECMO.

Our study has some limitations. Only autopsied lungs were included, with no specimens collected from living patients who had survived following ECMO treatment. This may have resulted in the overrepresentation of ECMO-related changes and findings associated with end-stage lung disease in our patients, such as fibrosis. Furthermore, we were not able to consider potentially confounding clinical factors influencing histopathologic changes in the lungs, such as ventilator settings, mode of mechanical ventilation, the presence of sepsis or septic shock, or other complications. Additionally, the study included a heterogeneous group of adult ECMO patients, and non-ECMO controls were retrospectively compared to VV ECMO recipients. Moreover, the number of lung autopsies from VV ECMO–treated patients was relatively small (n = 18), although it is the largest among studies published to date. Lastly, the controls were not perfectly age matched.

CONCLUSIONS

The results underline the wide variety of histopathologic findings in patients managed with ECMO. Some observations, such as DAD, seem to be associated with underlying disease and extended ECMO treatment. The data show that, although DAD was significantly more common in lung autopsies of VV ECMO patients, one-third of VA ECMO patients had histopathologic changes characteristic of ARDS.

As such, further research are required to confirm that the presence of DAD in lung autopsies of patients treated with VA ECMO indicates the need for protective lung ventilation in these patients.

Pulmonary hemorrhage was associated with a shorter ECMO duration and female sex, which suggests that it was caused by an underlying disease rather than ECMO therapy. Intriguingly, ECMO treatment was associated with a lower

Figure 2. Representative photomicrographs of pulmonary histopathologic findings. A, Upper-right shows pink, amorphous hyaline membranes. Slightly below, inflammatory infiltration with small lymphocytes and granulocytes, and larger histiocytes, fill 2 alveoli. On the left, pulmonary alveoli containing exudative fluid, single inflammatory cells, and hyaline membranes. B, Pink amorphous hump representing hyaline membrane separates internal alveolar lumen from septal elements, especially intraseptal capillaries. Additionally, intraseptal edema with an admixture of inflammatory cells increases the distance between the alveolar space and alveolar vasculature. C, Recent fibrotic phase of diffuse alveolar damage. An increase of green-stained collagen inside lung parenchyma (especially septa) and remnant red-brown hyaline membranes. D, Lung hemorrhagic infarction. Alveolar septa became necrobiotic and poorly visible. Inside the alveoli, numerous extravasated erythrocytes are seen. Inside alveoli reside erythrocytes, histiocytes containing gold-brownish hemosiderin granules, and punctiform black dust particles—siderophages (hematoxylin-eosin, original magnifications $\times 80$ [A] and $\times 400$ [B and D]; Masson trichrome, original magnification $\times 80$ [C]).
risk of interstitial edema and a higher incidence of bronchopneumonia than conventional management in ARDS patients. Taken together, our observations provide information about pulmonary disease in patients treated with ECMO that may help to prevent complications and improve patient outcomes.

References


