Insult to Injury: Development of Alveolar Hemorrhage after Initiation of Extracorporeal Membrane Oxygenation

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ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO) is associated with complications that are separate from the underlying diagnoses that require its use. One of the foremost complications of ECMO is a high incidence of bleeding, including alveolar hemorrhage (AH), which is believed to be due to both prophylactic anticoagulation and critical illness-induced systemic coagulopathy. However, akin to systemic inflammatory response syndrome after cardiopulmonary bypass, ECMO causes widespread systemic inflammation and acute lung injury, which likely further predisposes patients to AH. The burden of clinically significant AH among patients on ECMO for advanced lung disease remains unknown.

Patients and methods: Charts of patients with advanced lung disease who required ECMO at a single institution were reviewed. The clinical course and variables of patients who developed AH and those who did not were compared.

Results: This report describes five patients who developed AH after initiation of venovenous ECMO for refractory hypoxemia. Clinical and laboratory variables did not predict the development or the prognosis of AH. Two of these patients with refractory hypoxemia and AH were treated with pulse-dose corticosteroids, with a dramatic response in one case.

Conclusion: The acute decompensation of the patients and response to corticosteroids suggest AH was mediated by a systemic inflammatory process, as opposed to coagulopathy alone. Judicious use of steroids may be considered among select patients who develop AH without symptoms of systemic coagulopathy after initiation of ECMO.

Keywords: Acute lung injury, Alveolar hemorrhage, Extracorporeal membrane oxygenation.

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO), an intensive procedure reserved for gravely ill patients with refractory circulatory dysfunction, hypoxia, or hypercarbia, is known to be associated with several complications. As ECMO is used in critically ill patients, it is often difficult to distinguish the natural history of end-stage disease from complications related to ECMO. Yet, recent increases in the utilization of ECMO as a bridge to recovery or transplantation have brought to light, various complications that were previously not well characterized.¹

All patients on ECMO have a high risk of bleeding complications, particularly among those on venoarterial (VA) ECMO when compared with venovenous (VV) ECMO.² Patients’ propensity toward bleeding is believed to be due to systemic coagulopathy secondary to prophylactic heparinization³ as well as qualitative and quantitative platelet defects induced by high flow rates in the ECMO circuit which induces mechanical platelet trauma.⁴⁻⁶ These coagulopathies may lead to bleeding from any site, including the lungs. Pulmonary hemorrhage may result from insult to the bronchial vessels, pulmonary vessels, or the microcirculation; injury to the microcirculation results in intraalveolar accumulation of red blood cells and leads to the clinical syndrome of alveolar hemorrhage (AH).⁷ In a recent autopsy-based study, evidence of pulmonary hemorrhage was found in the majority of patients who died after being on ECMO for a mean duration of 7 days.⁸ These patients on VA-ECMO for cardiac indications without any premorbid pulmonary disease also had histologic evidence of acute lung injury (ALI). The high incidence of pulmonary hemorrhage and ALI suggests a common mechanism to both disease states, although it is unclear if systemic coagulopathy caused pulmonary hemorrhage and resultant lung injury or if ALI was the primary insult that then provoked hemorrhage. Despite the high prevalence of pulmonary hemorrhage on autopsy, the burden of clinically significant AH, especially among patients with underlying pulmonary disease, is not known.

Herein, we report a series of five patients on ECMO for refractory hypoxemia who developed an acute clinical syndrome of AH after initiation of ECMO. We compare the characteristics of these patients to patients on ECMO for refractory hypoxemia who did not develop AH and evaluate their outcomes.

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**Patients and Methods**

**Subjects**

The institutional ECMO database at the University of Texas Southwestern Medical Center in Dallas, Texas was reviewed to identify patients. Patients with advanced lung disease who needed VV- or VA-ECMO support between January 2013 and July 2015 were reviewed. Patients who did not survive at least 24 hours after the initiation of ECMO initiation were excluded (n = 1). Institutional review board provided approval for the study with a waiver of patient consent (IRB# STU 072015-001).

All patients were on VV- or VA-ECMO for respiratory failure. The VA-ECMO access was through the right axillary artery and the internal jugular vein; whereas all patients on VV-ECMO had Avalon® dual lumen cannula inserted via the right internal jugular vein approach. All patients were on unfractionated heparin drip at rates titrated to maintain activated clotting time (ACT) between 140 and 180 seconds for patients on VV-ECMO and 180 and 220 seconds on VA-ECMO. All patients were intubated and supported on mechanical ventilation at the time of ECMO initiation. Lung protective ventilator strategies consisting of low tidal volumes (6–8 mL/kg ideal body weight) and high positive end-expiratory pressure (8–15 cm H2O) were utilized.

**Variables**

Charts were reviewed for patient demographics, clinical and laboratory variables before and after initiation of ECMO, daily PaO2/FiO2 (P/F) ratios, and development of organ dysfunction during ECMO support. Patients on ECMO who survived to undergo lung transplantation (LT) were deemed to have a successful bridge to LT. The hospital survival for all patients was also recorded.

**Diagnosis of Alveolar Hemorrhage**

The diagnosis of AH was suspected among patients with a clinical and radiological presentation consisting of bloody return on endotracheal tube suctioning, drop in hemoglobin, and new pulmonary infiltrates. The diagnosis was confirmed upon the finding of progressively bloody return, and rising red blood cell counts on serial bronchoalveolar lavage aliquots from a particular location.9 Serial bronchoalveolar lavages were performed for confirmation only among patients in whom AH was clinically suspected based on above criteria.

**Statistical Analysis**

Data were described using proportions and median with the inter-quartile range as appropriate. Variables were compared between patients who developed AH and those who did not using the Mann–Whitney U test for continuous variables and Chi-squared test for categorical variables. Statistical significance was considered at p < 0.05 (two-tailed only).

**Results**

A total of 37 patients were on ECMO for refractory hypoxemia. Among these, 25 patients (67.6%) were placed on ECMO as a bridge to LT. The remaining 12 patients remained on ECMO as a bridge to recovery for severe pneumonia (n = 6), transplant rejection (n = 3), chemotherapy-related ALI (n = 2), and posthemorrhage repair aspiration pneumonia (n = 1). None of the patients on ECMO as a bridge to recovery were transplant or retransplant candidates. VA-ECMO was used for only five patients, who had comorbid pulmonary hypertension with right ventricular dysfunction. The remaining patients (n = 32) were on VV-ECMO. All patients underwent airway examination with bronchoscopy at least once after being placed on ECMO. None had evidence of AH prior to ECMO initiation. Five patients were diagnosed with AH based on the progressively bloody return and rising red blood cell counts on serial bronchoalveolar lavage aliquots (overall incidence 5/37, 13.5%). The majority of the patients who developed AH were females (n = 4). Three were bridging to transplant with an underlying diagnosis of acute exacerbation of interstitial lung disease. The remaining two patients were on ECMO due to refractory hypoxemia secondary to acute respiratory distress syndrome (ARDS) from massive aspiration and chemotherapy for breast cancer. The baseline characteristics, laboratory profile, and outcomes of the patients with and without AH are presented in Tables 1 and 2.

All patients who developed AH were noted to decompensate between 24 and 72 hours after ECMO initiation. None of the patients with AH were noted to have supratherapeutic-activated clotting times, dysfibrinogenemia, extrapulmonary bleeding at the time of diagnosis of AH, or other evidence of systemic coagulopathy apart from heparinization. Platelet counts in patients with AH and those without AH were similar. Further, none of the patients had evidence of active infection or clinically significant noncardiopulmonary organ dysfunction. Although they had marked the elevation of C-reactive protein, antineutrophil cytoplasmic antibody panel was negative in all five patients. Hemorrhage necessitated packed red blood cell transfusions among four patients.

After the development of AH, three patients developed profound worsening hypoxemia with P/F ratio <50 despite maximal support on ventilator and ECMO, necessitating the use of rescue therapies including inhaled nitric oxide and paralytics. The heparin infusion was discontinued in the four patients on VV-ECMO, while the ACT target was reduced to 140–180 seconds for the patient on VA-ECMO. Given their precarious clinical status and the lack of evidence of systemic coagulopathy, two of the three patients with refractory hypoxemia were treated with methylprednisolone 7.5 mg/kg/day for 3 days. A significant improvement in infiltrates and oxygenation was noted in one patient (Fig. 1), whereas the clinical status remained unchanged in the other.

Development of multiorgan dysfunction led to palliative extubation and decannulation in two patients, while three patients survived to hospital discharge. The explant pathology on patients with AH who were bridged to LT (n = 2) revealed bilateral hemorrhagic foci throughout on gross appearance (n = 1) with evidence of extensive diffuse alveolar damage (n = 2). Family of the two patients who did not survive to lung transplant declined an autopsy.

**Discussion**

Patients who developed AH after ECMO initiation overall did not have significant differences in their baseline profile or laboratory variable when compared with patients who did not have AH, although extensive analysis of variables is limited by the small number of cases. Not surprisingly, patients with AH tended to have a larger drop in their P/F ratio 24 hours after initiation of ECMO than patients who did not develop AH. This likely affected their ability to rehabilitate. Also, as a cohort, the patients with AH had higher post-ECMO lactate than those without AH. In particular, there were no differences in markers of coagulopathy or distribution of the underlying diagnosis to suggest why the five patients developed
AH. Patients with AH tended to have worse oxygenation despite negative fluid balance after ECMO initiation, which likely impacted their ability to rehabilitate. However, none of the variables achieved statistical significance and eventual outcome (successful bridge to recovery or LT) was not impacted.

This is the first case series that details clinically evident AH presenting with acute decompensation among adult patients shortly after the initiation of ECMO. Our report is similar to one study of pediatric patients who developed AH in the absence of systemic coagulopathy while on ECMO although, in contrast to the current study, this syndrome developed more frequently in patients who had evidence of multi-organ dysfunction before ECMO initiation. In a recent study, autopsy evidence of AH was noted in 68% of the pediatric and adult patients who died shortly after or while on ECMO, although it remains unknown how many of the patients in this series had clinical evidence of AH and how it impacted their clinical course. It included a heterogeneous population with many pediatric patients, and a large majority of the population was on VA-ECMO for cardiac indications. In addition, patients in the above-mentioned study were on ECMO for a mean duration of 7 days, whereas patients in our series developed clinical signs of AH within 24–72 hours of ECMO initiation. This suggests that ECMO-associated AH may present in phenotypes of differing severity, perhaps related by varying etiologies such as coagulopathy (induced or as part of systemic disease), cardiac dysfunction, underlying pulmonary disease, age, or systemic inflammatory response syndrome, which may or may not necessarily correlate with the clinical prognosis. Further, while pulmonary hemorrhage

| Variable                                      | Development of alveolar hemorrhage |
|-----------------------------------------------|-----------------------------------|
|                                               | Yes (n = 5) | No (n = 32) | p value     |
| Age                                           | 55 (51–69) | 53.5 (18–67) | 0.21       |
| Male sex                                      | 20%        | 62.5%        | 0.14       |
| Caucasian                                     | 40%        | 56.3%        | 0.8        |
| Underlying diagnosis necessitating extracorporeal membrane oxygenation (ECMO) | | | |
| Interstitial lung disease                      | 59.4%      | 60%          | 0.38       |
| Acute respiratory distress syndrome           | 18.8%      | 60%          | 0.46       |
| Transplant rejection                          | 9.4%       | 9.4%         | 1          |
| Cystic fibrosis                               | 6.2%       | 6.2%         | 1          |
| Others*                                       | 40%        | 40%          | 0.9        |
| Comorbid pulmonary hypertension**            | 20%        | 21.9%        | 0.71       |
| Right ventricular dilation on echo            |            |              |            |
| None                                          | 60%        | 59.4%        | 0.22       |
| Mild                                          | 40%        | 40%          | 1          |
| Moderate                                      | 25%        | 25%          | 1          |
| Severe                                        |            | 6.2%         |            |
| Right ventricular systolic dysfunction on echo|            |              |            |
| None                                          | 80%        | 62.5%        | 0.8        |
| Mild                                          | 20%        | 21.9%        | 0.6        |
| Moderate                                      | 20%        | 9.4%         | 0.5        |
| Severe                                        | 6.2%       | 6.2%         | 0.5        |
| Pre-ECMO transfusion                          | None       | 25%          | 0.6        |
| Pre-ECMO pressors                             | 20%        | 46.9%        | 0.6        |
| Pre-ECMO BiPAP use                            | 60%        | 71.9%        | 0.57       |
| Pre-ECMO mechanical ventilation               | 100%       | 100%         | 1          |
| Pre-ECMO use of inhaled nitric oxide          | 80%        | 68.8%        | 0.53       |
| Pre-ECMO-positive blood cultures              | None       | None         |            |
| Use of paralytics prior to ECMO               | 20%        | 15.6%        | 0.61       |
| Venovenous-ECMO                               | 80%        | 87.5%        | 0.54       |
| Successful bridge to lung transplantation (LT)| 66.7%      | 59.1%        | 0.65       |
| Intended bridge to LT                         | 60%        | 68.8%        | 0.53       |
| Able to get out of bed before transplant      | 0          | 54.5%        | 0.22       |
| Able to ambulate before transplant            | 0          | 22.7%        | 0.5        |
| Successful bridge to LT                       | 66.7%      | 59.1%        | 0.65       |

Continuous variables were compared using the Mann–Whitney U test, and Chi-squared test was used for categorical variables

* n = 5. Includes two patients with chemotherapy-related acute lung injury, and one patient each with pulmonary hypertension, COPD, and posthernia-repair aspiration pneumonia (AH group)

**Pulmonary hypertension based on right heart catheterization
ECMO-associated Alveolar Hemorrhage

Table 2: Laboratory variables before and after extracorporeal membrane oxygenation (ECMO) initiation among patients with and without the development of alveolar hemorrhage (AH)

|                      | Pre-ECMO | Post-ECMO |
|----------------------|----------|-----------|
|                      | Patients who developed AH | Patients who did not develop AH | Patients who developed AH | Patients who did not develop AH |
| Hemoglobin           | 9.3 (6.9–11.6) | 9.6 (6.4–15) | 6.6 (6.1–8.2) | 6.7 (5.8–10.5) |
| WBC                  | 13.7 (5.3–22.4) | 12.9 (3.7–35.6) | 86 (54–277) | 53.5 (43–278) |
| Platelets            | 209 (83–272) | 165 (85–542) | 6.6 (6.1–8.2) | 6.7 (5.8–10.5) |
| Creatinine           | 0.63 (0.32–0.88) | 0.65 (0.21–3.89) | 0.61 (0.34–0.99) | 0.93 (0.45–5.35) |
| Albumin              | 3.2 (2.9–3.4) | 2.85 (2–4.1) | 2.6 (2.2–3.5) | 2.55 (1.5–3.3) |
| ALT                  | 23 (19–165) | 36 (6–649) | 3.5 (0.9–20) | 1.7 (1.1–4) |
| Lactate              | 1.8 (1.6–5.6) | 1.6 (0.9–6) | 72 hours 69.5 (56–423) | 24 hours 93 (35–370) |
|                      |           |           | 48 hours 62 (44–131) | 48 hours 78 (50–200) |
|                      |           |           | 72 hours 69 (47–202) | 72 hours 88 (43–314) |
|                      |           |           | 96 hours 67 (42–135) | 96 hours 86 (56–295) |
| P/F ratio            | 116 (88–395) | 88 (46–336) | 24 hours 69.5 (56–423) | 24 hours 93 (35–370) |
|                      |           |           | 48 hours 62 (44–131) | 48 hours 78 (50–200) |
|                      |           |           | 72 hours 69 (47–202) | 72 hours 88 (43–314) |
|                      |           |           | 96 hours 67 (42–135) | 96 hours 86 (56–295) |
| Net fluid balance (mL) 72 hours post-ECMO | –412 (–4,241 to 8,182) | 1,026 (–6,545 to 8,603) | 412 (–4,241 to 8,182) | 1,026 (–6,545 to 8,603) |

Continuous variables were compared using the Mann–Whitney U test and Chi-squared test was used for categorical variables. Variables that met statistical significance (p ≤ 0.05) are shown in bold.

Figs 1A to D: Serial chest radiographs of a patient with alveolar hemorrhage and acute respiratory distress syndrome: (A) On the day of placement of extracorporeal membrane oxygenation (ECMO) cannula; (B) 36 hours after ECMO initiation, showing worsening of bilateral opacities; (C) Bronchoalveolar lavage return on serial instillations of saline from the right middle lobe. Bronchial wash collected in the trap during the procedure is observed in the background (arrow); (D) Five days after initiation of pulse corticosteroids.

may be a common postmortem finding, particularly in patients less than a year old on VA-ECMO, our series suggests that clinically significant AH is less prevalent. The true burden of AH on ECMO is likely overestimated in the above-mentioned autopsy study by virtue of inclusion being limited to patients who did not survive. While prognostic data cannot be extrapolated from this case series, patients who developed AH had an acceptable survival to discharge, implying ECMO-induced AH does not signal imminent death.

The etiological mechanism behind ECMO-associated AH in the absence of evidence of disseminated intravascular coagulopathy or extrapulmonary bleeding remains uncertain. The favorable response to pulse doses systemic corticosteroid in one of the patients in the current series was intriguing as it supports the widespread immune activation and autoimmune injury as the etiological basis in some of these patients with ECMO-associated AH. When a patient’s blood comes in contact with the
nonendothelialized surface of the ECMO circuit, a widespread inflammatory cascade is triggered. Proinflammatory cytokines, coupled with concurrent activation of complement, leukocytes, platelets, and the coagulation cascade, rise dramatically within minutes from initiation of ECMO.\textsuperscript{11,12} These inflammatory mediators induce neutrophil activation and infiltration, which is thought to be responsible for end-organ damage associated with ECMO.\textsuperscript{13} Among patients on ECMO for pulmonary indications, the lungs may be particularly vulnerable to insult given their diseased state at ECMO initiation, ongoing ventilator-induced barotrauma, and preexisting systemic inflammation from the critical illness. Due to the mechanisms described above, initiation of ECMO may lead to a compounding of the preexisting ALI, which may progress to ARDS and AH. Given the lack of description of ECMO-induced AH, we draw a parallel to systemic inflammatory release syndrome seen after cardiopulmonary bypass (CPB), which also plays a role in pulmonary dysfunction.\textsuperscript{14,15} Following CPB, pneumocytes and endothelial cells become swollen and necrotic, leading to decreased compliance, increased vascular resistance, and changes in lung surfactant.\textsuperscript{16} In addition, lung permeability is likely increased in this setting, placing the lungs at an even greater risk for inflammatory-mediated injury.\textsuperscript{17}

It is concluded that a significant proportion of patients on VA- and VV-ECMO for pulmonary indications may develop spontaneous AH. This syndrome is characterized by worsening pulmonary infiltrates and progressive hypoxemia in the setting of elevated serum inflammatory markers, and is often significant to the degree that it requires blood transfusions. While this complication of ECMO initiation may have different phenotypes and its etiological basis may be multifactorial, activation of the innate inflammatory cascade by the ECMO circuit is likely to be a significant contributor. This theory is supported by the lack of extrapulmonary bleeding or dysfibrinogenemia, the presence of an elevated C-reactive protein, and the brisk response to pulse steroids to one of the patients in the current report. Further, clinical and laboratory variables do not predict the development of AH or the prognosis. The current series demonstrates that despite worse morbidity, these patients have the potential to recover to discharge from the hospital, both with and without a lung transplant.

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