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Original Article

# Single-Center Experience With Venovenous ECMO for Influenza-Related ARDS

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*Objectives:* This study was designed to determine whether venovenous extracorporeal membrane oxygenation (VV ECMO) reduced mortality in patients with influenza-related acute respiratory distress syndrome (ARDS).
*Design:* A retrospective cohort study was performed. Baseline characteristics of participants were compared and Kaplan-Meier survival analysis was used to compare survival at last medical center follow-up. Cox proportional hazards modeling also was performed to test for univariate associations between salient variables and mortality.
*Setting:* A single-center ECMO referral university hospital.
*Participants:* All patients admitted with influenza-related ARDS during the 2015 to 2016 influenza season.
*Interventions:* Mechanical ventilation alone versus mechanical ventilation and ECMO cannulation.
*Measurements and Main Results:* A total of 26 patients with influenza-related ARDS were included in the cohort. Thirteen patients were treated with VV ECMO while 13 were not. Twelve of the ECMO patients and 8 of the non-ECMO patients were transferred from outside hospitals. Patients treated with ECMO were younger and had less hypertension and diabetes mellitus. There was no difference in baseline sequential organ failure assessment score between the 2 groups. In-hospital mortality for ECMO patients was 15.4% versus 46.7% for patients not treated with ECMO. Survival at last medical center follow-up was better in patients treated with ECMO ($p = 0.02$). Age, highest blood carbon dioxide level, and treatment without ECMO were all associated with increased mortality.
*Conclusions:* Influenza-related ARDS has a high mortality rate and patients treated only with mechanical ventilation have worse outcome than those managed with VV ECMO. More liberal use of ECMO should be considered in patients with influenza-related ARDS.


*Key Words:* ARDS; ECMO; influenza; mechanical ventilation

IN 2009, the impact of pandemic Influenza A (H1N1) pdm09 on the general population was limited, but a small number of patients developed severe acute respiratory distress syndrome (ARDS).[1,2] Adults hospitalized during this period were younger and had fewer comorbidities than those admitted during usual seasonal influenza epidemics.[2] In 2013 to 2014, H1N1 was again a predominant influenza strain, and similar epidemiology for ARDS was seen leading to significant morbidity and mortality in a select group of patients.[1–4]

In both seasons, patients with severe ARDS were managed with venovenous extracorporeal membrane oxygenation (VV ECMO) at some centers, but the use of VV ECMO remains

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controversial and has not been universally adopted for severe ARDS.[5] Most patients with ARDS who die have multiorgan system failure, but almost half of H1N1-associated deaths are related to severe impairment in gas exchange.[6] It has been suggested that patients with H1N1-associated ARDS may benefit disproportionately from ECMO because they tend to be younger and are more likely to have organ recovery.

In 2009, the Australian and New Zealand Intensive Care Society (ANZICS) described 68 adult patients who were treated with VV ECMO for influenza-related ARDS.[5] VV ECMO patients were younger and more likely to require vasopressors, but they also had more severe ARDS. The study did not demonstrate a survival benefit with VV ECMO, but overall survival in the ECMO group was better than expected given the degree of severe gas exchange impairment. In comparable cohorts, mortality had been as high as 50% with conventional mechanical ventilation only.[7] In a United Kingdom study where H1N1-related ARDS patients were referred to an ECMO center, a 29% mortality reduction was seen compared to controls.[8] Several other studies have supported VV ECMO's potential benefits in severe ARDS.[8–10] Not all studies, however, have shown a mortality benefit with ECMO. In a recent French study, Pham et al found no difference in patient outcomes when VV ECMO was compared against mechanical ventilation.[11]

In 2015 to 2016, H1N1 re-emerged and led to a surge in patients with influenza-related ARDS requiring mechanical ventilation. Given that the use of VV ECMO remains controversial, the study purpose was to critically evaluate outcomes for adult patients who were treated with VV ECMO compared to those treated with conventional mechanical ventilation in the authors' ECMO referral medical center. The authors hypothesized that the use of VV ECMO would be associated with improved survival.

## Patients and Methods

### *Patients*

All adult patients ($>18$ years old) with laboratory-confirmed influenza who were admitted to the authors' medical center between November 1, 2015 and April 30, 2016 were identified using the hospital's infection control database. Polymerase chain reaction assay was used to confirm influenza in all patients. Patients that required mechanical ventilation were identified using electronic medical records. A diagnosis of ARDS was confirmed in these patients using the Berlin definition for ARDS.[12] The final study cohort included all influenza patients admitted to the medical center with ARDS during the 2015 to 2016 season. The University of Maryland, Baltimore Institutional Review Board approved the study protocol.

### *Patient Data*

For all patients in the cohort, the authors collected the following demographic and medical variables: age, sex, presence of baseline comorbidities including hypertension, diabetes mellitus, chronic lung disease (defined as chronic obstructive pulmonary disease, asthma, or restrictive lung disease), active smoker (defined as tobacco use within 14 days), coronary artery disease (defined as prior percutaneous coronary intervention, prior coronary artery bypass grafting, or history of angina or myocardial infarction), and congestive heart failure (defined as either systolic or diastolic dysfunction).

Disease-state data included: influenza infection (A or B), influenza vaccination status for the studied season, sequential organ failure assessment (SOFA) score during the first 24 hours of hospitalization, mode of mechanical ventilation, Murray score at time of intubation, lowest partial pressure of oxygen ($pO_2$)/fraction of inspired oxygen ($F_IO_2$) ratio during mechanical ventilation, highest partial pressure of carbon dioxide ($F_IO_2$) during mechanical ventilation, highest $pCO_2$ during mechanical ventilation, highest positive end expiratory pressure during mechanical ventilation, and lowest pH during mechanical ventilation. The authors also collected data on VV ECMO consultation and use, prone positioning, and the use of inhaled pulmonary vasodilators.

Further, outcome data were collected including: total mechanical ventilation days, total hospital days, major bleeding events (defined as bleeding that required surgery or transfusion of at least 2 units of red blood cells), bacterial superinfection, stroke, pneumothorax, renal failure requiring renal replacement therapy, 30-day mortality, and in-hospital mortality.

### *ECMO and Mechanical Ventilation Details*

The University of Maryland Medical Center is a regional ECMO referral center with over 500 adult ECMO runs during the last 5 years. Since 2014, adult VV ECMO has been standardized and primarily cared for in a dedicated Lung Rescue Unit. Percutaneous insertion of an inflow cannula into the common femoral vein and outflow cannula into the right internal jugular vein is typically employed. A Rotaflow (Maquet, Wayne, NJ) centrifugal pump and Quadrox oxygenator (Maquet) were used. Anticoagulation during ECMO is with unfractionated heparin and the goal-activated partial thromboplastin time is between 45 and 55 seconds. Patients receive protective lung ventilation while on ECMO. Typical ventilator settings are a driving pressure of 10 $cmH_2O$ and positive end expiratory pressure (PEEP) of 10 $cmH_2O$ using pressure-controlled ventilation. Patients who were not on ECMO received protective mechanical lung ventilation with tidal volumes of 6 mL/kg and plateau pressure less than 30 $cmH_2O$. The same ventilation parameters were used in ECMO patients prior to cannulation.

A multidisciplinary team composed of cardiac surgeons and intensive care physicians performs evaluation for ECMO in the authors' center. Patients with severe ARDS that are referred from outside hospitals are routinely evaluated for ECMO when they arrive at the hospital's critical care triage unit, while patients already admitted to the hospital who develop ARDS

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