Trends in extra-corporeal membrane oxygenation for the treatment of acute respiratory distress syndrome in the United States

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Introduction

The acute respiratory distress syndrome (ARDS) is a state of diffuse inflammatory lung injury characterized by acute-onset, non-cardiogenic pulmonary edema with varying degrees of hypoxemia. Despite significant advances in intensive care, mortality from ARDS remains high.[1–5] To date, the only interventions that have been shown to improve survival in ARDS are low tidal volume ventilation and prone positionin.[6,7]

The use of extra-corporeal membrane oxygenation (ECMO) for the treatment of ARDS has received significant attention in the past decade. ECMO allows for extra-pulmonary gas exchange and very low tidal volume ventilation, “resting” the heart and lungs and buying time for treatment and recovery in cardiorespiratory failure. The 2014 Extra-corporeal Life Support Organization (ELSO) guidelines suggest that ECMO be considered in patients with high-risk hypoxic or hypercarbic respiratory failure despite optimal conventional ventilation.[8] However, the role of ECMO in ARDS remains undefined.

The 2012 ELSO registry report indicates increased use of ECMO for all-cause respiratory failure in the wake of the 2009 H1N1 influenza pandemic, but does not provide information about patient characteristics associated with ECMO use; nor does it focus on ARDS specifically.[9] The goal of our study was to examine patterns of ECMO use for the treatment of ARDS in the United States between 2006 and 2011.

Materials and Methods

We report our study in according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[10] A waiver of consent was obtained from the University of British Columbia Institutional Review Board.

Study Population

For this retrospective cohort study, data from the Nationwide Inpatient Sample was examined for the years 2006-2011. This nationally representative dataset captures approximately 20% of all United States hospital discharges. It is a complex survey designed to produce national projections released by the Agency for Healthcare Research and Quality (AHRQ).

The cohort was obtained by isolating all patients greater than 18 years of age who had a discharge diagnosis of ARDS. ICD9 codes for acute respiratory failure following trauma and surgery (518.51), other pulmonary insufficiency, not elsewhere classified, following trauma and surgery (518.52), acute and chronic respiratory failure following trauma and surgery (518.53), acute respiratory failure (518.81) and other pulmonary insufficiency, not elsewhere classified (518.82) were used to define ARDS, consistent with definitions of previous authors.[11] Patients who had ICD9 procedure codes for ECMO (39.65 and 37.62) were then segregated from the overall ARDS group. A flow diagram of patient selection is displayed in Figure 1. We also queried for the use of inhaled nitric oxide (00.12).

Patient level factors gathered included age, gender, race (White, Black, Hispanic, other or missing), length of stay, hospital mortality, insurance status (coverage vs no coverage), and patient zip code income quartile. Hospital characteristics obtained included teaching status (teaching vs non-teaching), size (as defined by the AHRQ), and region of the country (Northeast, Midwest, South, West).

Statistical Analysis

Data were analyzed using complex survey procedures in SAS version 9.4 (SAS Institute, Cary, NC); national estimates were obtained with appropriate national weights. Chi-squared tests were used for nominal or ordinal outcomes; independent t tests were used for continuous data. Trend analysis was performed using linear regression. All tests were performed at an alpha level of 0.05.

Results

A total of 47,911,414 hospital discharges were examined, representing 235,911,271 hospitalizations using national weights. There were 1,479,022 discharges that met the definition of ARDS, representing 7,281,206 discharges. There were 775 patients with a diagnosis of ARDS who underwent ECMO during the study period (Table 1). Overall in-hospital mortality for the ECMO group was 58.6% versus 25.1% in the non ECMO cohort ($p = <0.0001$). Length of stay was longer for patients who underwent ECMO, 15.8 (IQR 28.5) days vs 6.9 (IQR 10.3) days ($p=<0.0001$). Patients treated with ECMO were younger, at 47.9 (SD 16.8) years vs 66.4 (SD 16.9) years ($p=<0.0001$), as well as less likely to be female, 37.7% vs 50.4% (p=<0.0001). There was no difference in the use of ECMO by zip code income quartile. Hospital characteristics associated with the use of ECMO included teaching status (92.0% vs 45.6% p=<0.0001) and large hospital size (86.7% vs 64.9% p=<0.0001). The region of the country where care was delivered was not significant (p=0.11).

The trend in the use of ECMO for ARDS is displayed in Figure 2. There was a 409% relative increase in the use of ECMO for ARDS in the United States between 2006 and 2011, from 0.0177% to 0.0901% (p=0.0041).

Discussion

There has been a dramatic increase in ECMO use for the treatment of ARDS in the United States. Patients who receive ECMO are young males who have higher in-hospital mortality and are more likely to be treated in large teaching hospitals compared to those that do not receive ECMO.

The increase in ECMO use seen in our study is consistent with ELSO registry data.[9] There are several possible reasons for the dramatic uptake in use. Most significantly, the successful use of ECMO in severe cases of ARDS during the H1N1 influenza epidemic, and the ensuing attention in the literature, led to renewed interest in the therapy.[12–17] Furthermore, significant refinements in ECMO technology since its inception allow for easier, safer, and more widespread use.[18]

Our finding that young males are more likely to receive ECMO is consistent with scoring models proposed to estimate survival probability in

ECMO patients, which show that both younger age and male gender are associated with improved survival.[19,20] Patients who receive ECMO are more likely to be treated in large, tertiary academic hospitals is unsurprising given the resource-intensive, highly-specialized nature of the therapy.

The 59% percent mortality rate in ECMO patients in our study is concurrent with the latest ELSO registry paper, which showed a 51% mortality rate in adult patients undergoing VV-ECMO for ARDS.[9] Other publications of heterogeneous study populations have reported a very wide range of mortality in ECMO-treated ARDS patients, ranging from 16% to 64%.[17] The finding that ECMO patients have a higher mortality rate than the control group in our study is highly susceptible to selection bias, as it is usually the sickest patients who receive ECMO as a rescue measure.

The role of ECMO for ARDS remains hotly debated.[21,22] Several recent meta-analyses cite insufficient high-quality evidence, as there is a paucity of well-designed randomized control trials, particularly in the current era of lung-protective ventilation.[17,23] The CESAR trial seemed to support transfer to an ECMO-capable center for patients with severe ARDS, but results should be interpreted with caution given the lack of standardized therapy in the control group and differences in rates of lung-protective ventilation.[24] Studies are underway that will hopefully provide more definitive answers about the role of ECMO and extra-corporeal CO2 removal in treating ARDS.[14,25]

The strength of our study lies in the use of a large, nation-wide dataset capturing 20 percent of all hospital admissions. This allows for excellent generalizability and accurate representation of the use of ECMO for ARDS in the United States.

The results of our study need to be interpreted in the context of the study design. Retrospective observational studies based on discharge data are inherently susceptible to patient selection bias, as well as the possibility of coding errors. Furthermore, we were unable to collect data on patient-level variables including etiology of ARDS, which may influence outcomes. Further high-quality trials are needed to clarify the role of ECMO in ARDS.

Conclusions

The use of ECMO for the treatment of ARDS in the United States increased by over 400% between 2006 and 2012. Patients who receive ECMO are more likely to be younger males, and to be treated in large tertiary care hospitals. Mortality for the ECMO-treated group was 59%. Further research is needed to clarify the role of ECMO in treating ARDS.

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