KEYWORDS:
Extracorporeal membrane oxygenation; ARDS; H1N1; Volume Diffusive Respirator; VDR; ELSO

Abstract
BACKGROUND: The investigators compared a series of adult survivors of severe H1N1 pneumonia treated with extracorporeal membrane oxygenation (ECMO) with members of the Extracorporeal Life Support Organization registry for patients with H1N1 with regard to ventilator management while on ECMO.

METHODS: Adults who survived ECMO were compared regarding time on ECMO for those treated with the Volume Diffusive Respirator (VDR) or with conventional “lung rest.” The VDR delivered 500 percussions/min, with tidal pressures of 24/12 cm H2O and a fraction of inspired oxygen of .4 at 15 beats/min.

RESULTS: There were no differences between the study patients (n = 7) and the Extracorporeal Life Support Organization cohort (n = 150) regarding age, pre-ECMO ventilator days, pre-ECMO ratio of partial pressure of oxygen to fraction of inspired oxygen, or survival after lung recovery. Patients treated with VDR required ECMO support for a shorter duration (mean, 193.29 ± 35.71 vs 296.63 ± 18.17 hours; P = .029).

CONCLUSIONS: These data suggest that the VDR enhanced pulmonary recovery from severe H1N1 pneumonia in adults. Shorter times on ECMO may improve the risk/benefit and cost/benefit ratios associated with ECMO care.

At the extremes of lung failure, it becomes impossible to oxygenate and ventilate a patient. The ventilator itself can cause additional injury to the lung. Various strategies of protective ventilation have become standards of care, yet even these methods may fail to support a patient with the most severe manifestations of acute respiratory distress syndrome (ARDS). For many years, extracorporeal membrane oxygenation (ECMO) for adult ARDS was considered controversial because of early studies involving techniques that are no longer clinically relevant. Recent reports have suggested that patients cared for at ECMO centers have improved survival from generic ARDS and lung failure caused by the H1N1 virus.

Current controversy regarding the routine use of ECMO for ARDS is focused on 2 primary criticisms. First, the
efficacy of ECMO relative to aggressive use of the ventilator continues to be challenged.\textsuperscript{10,11} Second, concerns about the cost and safety of ECMO remain barriers to more widespread adoption. Any strategy that enhances lung recovery and decreases the time a patient requires extracorporeal support reduces both the cost and the risk of ECMO and enhances the cost/benefit and risk/benefit ratios of the therapy.

At our center, we provide aggressive multifaceted care for patients with ARDS. We use lung-protective ventilation with the Volume Diffusive Respirator (VDR; Percussionaire Corporation, Sand Point, ID). During the autumn of 2009, we treated a number of adults with H1N1 pneumonia with ECMO. Although the basic tenet of ECMO support for ARDS is predicated on using the circuit to support respiration and minimizing the ventilator to “rest settings” to eliminate ventilator-induced lung injury (VILI),\textsuperscript{12} we used the VDR with modest settings. These settings were chosen not to affect the gas exchange of oxygen or carbon dioxide but to facilitate pulmonary recovery through airway clearance of secretions, exudates, and blood; gentle alveolar recruitment and restoration of functional residual capacity. We report a single-center series of adults who required ECMO for refractory hypoxemic ARDS due to pandemic (2009) H1N1 pneumonia in comparison with a cohort of similar patients reported to the H1N1 registry of the Extracorporeal Life Support Organization (ELSO).\textsuperscript{13}

**Methods**

Our approach to the treatment of ARDS is based on a protocolized and evidence-based regimen focused on adequate oxygen delivery using the lowest possible levels of ventilator support.\textsuperscript{14} Specifics of our current regimen for patients requiring ECMO support have been described.\textsuperscript{15} Our center uses the full spectrum of ventilator modes, including airway pressure release ventilation and high-frequency ventilation. Our most advanced ventilator management uses the VDR-4 critical care ventilator, which is a high-frequency device that delivers pressure-controlled tidal ventilation and a simultaneous small-volume, high-frequency percussive component at a rate of 500 Hz (Fig. 1).

If, despite and after the above measures, a patient cannot achieve an $\text{PaO}_2/\text{FiO}_2$ ratio (PF ratio) (ratio of the partial pressure of oxygen [$\text{PaO}_2$] to the fraction of inspired oxygen [$\text{FiO}_2$]) $>100$ on “safe” settings (ie, $\text{FiO}_2 < 80\%$, peak inspiratory pressure $< 40$ cm H$_2$O, and tidal volume $< 6$ to $8$ cm$^3$/kg), the patient is considered for ECMO support. We follow the World Health Organization recommendation that the treatment of ARDS associated with the novel influenza A (H1N1) virus infection be based on evidence-based guidelines for sepsis-associated ARDS using low–tidal volume, lung-protective mechanical ventilation as the initial strategy. The protocol is designed to rapidly apply increasingly intense methods of pulmonary support and to identify patients who demonstrate failure to respond to ARDS Network\textsuperscript{16} ventilation strategies, airway pressure release ventilation, and the VDR while they are in the early stages of the H1N1 pneumonia, before VILI and secondary complications ensue.

Once adequate ECMO support is instituted, the ventilator is set to low “recruitment” settings. All patients are maintained with the VDR. VDR settings during ECMO support consist of $\text{FiO}_2$ of $40\%$, pulsatile flow rate (inspiratory pressure) in the mid–$20$ cm H$_2$O range, an oscillatory positive end-expiratory pressure (PEEP) of $12 \pm 2$ cm H$_2$O, a rate of $15$ cycles/min with an inspiratory/expiratory ratio of $1:1$, and a percussive frequency of $500$ beats/min. These lung-protective recruitment settings were not adjusted during the entirety of the ECMO course. As patients recover and “trials off” ECMO are initiated, a convective pressure rise and other adjustments are added to the ventilator management as clinically indicated.

When a patient begins to show evidence of pulmonary recovery, he or she is given a “trial off” consisting of a protocolized evaluation of a patient’s native pulmonary function. The ventilator is set for optimal levels of pulsatile flow rate and oscillatory PEEP, and inspired oxygen is set at $100\%$. Then the ECMO circuit gas exchange is stopped while flows are maintained. At this point, there is no extracorporeal oxygenation or carbon dioxide removal. If the patient’s hemodynamic status and gas exchange are adequate on the VDR, inspired oxygen on the ventilator is reduced to $50\%$. Patients are removed from ECMO support if their $\text{PaO}_2/\text{FiO}_2$ ratio is $>200$ with an $\text{FiO}_2$ of $50\%$ and pressures $<38$ cm H$_2$O. Beyond these parameters, we do not use the ventilator to correct carbon dioxide in patients weaning from ECMO. If mild to moderate respiratory acidosis persists, it is managed with the addition of bicarbonate or tromethamine drips that are titrated for a pH $>7.2$.

Data are reported as numbers, percentages, and mean $\pm$ SEM. All data are derived from the ELSO H1N1 registry reported on January 13, 2011, and comparisons of mean
values were performed using \( t \) tests. \( P \) values \(<.05 \) were considered statistically significant.

**Results**

Between October 2009 and January 2010, 15 patients with H1N1 pneumonia were treated with ECMO at Legacy Emanuel Health Center (LEH) in Portland, Oregon. Twelve of these were adults (aged \( >17 \) years; range, 26 to 59 years), 7 recovered lung function and were weaned from ECMO, and 6 survived to discharge. One patient died after recovery from cerebral hypoxia incurred before the initiation of ECMO support. The LEH patients (\( n = 7 \)) were compared with the ELSO cohort of adults who recovered (\( n = 135 \)) and who survived to discharge (\( n = 118 \)).

The surviving patients in the LEH series were 34.0 ± 2.45 years old, and 50% were men. Before the initiation of ECMO, they had been ventilated for 3.70 ± 1.6 days and had a mean \( \text{PaO}_2/\text{FiO}_2 \) ratio of 58.9 ± 5.5. There were no significant differences in these measures between the LEH patients and the ELSO cohort (Table 1).

LEH patients who recovered lung function and were weaned from ECMO spent 193.3 ± 35.7 hours on ECMO. This time is significantly shorter than the duration of ECMO for the ELSO patients, which was 296.6 ± 18.2 hours (\( P = .029 \)). The mean post-ECMO \( \text{PaO}_2/\text{FiO}_2 \) ratio measured within 24 hours of weaning from ECMO was 310.2 ± 26.2 in the surviving LEH patients. In both the LEH and ELSO cohorts, 86% of those who recovered to wean from ECMO survived to discharge.

**Comments**

The H1N1 pandemic generated a worldwide resurgence of interest in ECMO after the nearly simultaneous publication of a large clinical series describing the role of ECMO for H1N1 in the Southern Hemisphere and a prospective randomized trial reporting the benefit of referral to an ECMO center for adults with ARDS. The 2009 novel H1N1 influenza pandemic provided a large cohort of acutely ill, otherwise healthy patients with profound and isolated viral ARDS. The experience of the Australian and New Zealand investigators stimulated our center to increase both ECMO and advanced ventilation capabilities. Our most advanced ventilator was the VDR-4.

The VDR is a pneumatically powered, pressure-limited ventilator that delivers tidal breaths with a superimposed high-frequency, sub–tidal volume percussive component (high-frequency percussive ventilation [HFPV]). Typically, the tidal portion is provided at a rate of 15 cycles/min, and the inspiratory/expiratory ratio is 1:1. The high-frequency percussive aspect is provided by the ventilator and a flow interrupter called a Phasitron (Percussionaire Corporation) that delivers tiny (approximately 30 cm\(^3\)) percussive bursts of air at frequencies of 500 beats/min (range, 50 to 900 beats/min). Fig. 1 illustrates a typical waveform in which the end-expiratory pressure is labeled the “oscillatory PEEP,” the inspiratory pressure is called the “pulsatile flow rate,” and an optional additional pressure increase is called the “convective pressure rise.”

In animal models of aspiration and inhalation injury, HFPV has been shown to improve both oxygenation and carbon dioxide clearance while decreasing histologic evidence of lung injury and chemical evidence of inflammation. Clinical studies in burn and trauma patients have demonstrated improved oxygen indices, \( \text{PaO}_2/\text{FiO}_2 \) ratios, ventilation, and compliance relative to conventional ventilation modes in both retrospective observational reviews and prospective, randomized trials.

The mechanisms by which HFPV improves oxygenation, recruits atelectatic segments, and mobilizes secretions without increasing VILI involve both the tidal respirations and the high-frequency, low-volume percussions. Specifics of VDR ventilation are related to longitudinal dispersion, bulk flow, pendelluft, and laminar flow for the high-frequency components and a general increase in mean airway pressure without increasing peak pressures for the low-frequency tidal breaths. HFPV has been most widely adopted in burn care, for which the clearance of thick secretions and debris is critical. Application to the dense consolidation of profound H1N1 pneumonia (Fig. 2) was a natural extension of our experiences with ARDS in pediatric, septic, burn, and trauma patients.

The current standards for ventilator management for adult ARDS patients on venovenous ECMO recommend “lung rest” during ECMO support. The rationale for this approach is that the lung itself is unable to provide essential oxygenation and/or ventilation functions, and to persist with aggressive ventilation increases the risk for VILI without any benefit. Venovenous ECMO itself does not treat ARDS or its causes. It merely provides gas exchange while the initiating source is identified and treated if the lungs are

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<td>Hours spent on ECMO</td>
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to heal. The standards for “lung rest” involve reducing the ventilator pressure and decreasing inspired oxygen. ELSO recommends that this involve a pressure control mode, PEEP of 10 to 15 cm H₂O, peak airway pressures of PEEP + 10 cm H₂O, an FiO₂ of 30%, and a respiratory rate of 10 beats/min. The settings we chose as “rest settings” on the VDR closely reflect the above recommendations (pressures of 24/12 cm H₂O, a rate of 15 cycles/min with an inspiratory/expiratory ratio of 1:1, and FiO₂ of 40%), with the exception that we used the VDR and a superimposed percussive rate of 500 beats/min. The addition of the percussive component was designed to gradually recruit available functional residual capacity, limit secondary atelectasis, mobilize secretions, and facilitate lung recovery.

Numerous other series of ECMO for adult H1N1 have been published. Our patient time on ECMO of 193 hours (8 days; range, 3 to 15 days) compares favorably with the reports of the Italian (9 days; range, 7 to 15 days), Japanese (9 days; range, 6.5 to 12.5 days), Australian and New Zealand (10 days; range, 7 to 15 days), Canadian (15 days; range, 14 to 15 days), Swedish (16 days; range, 9.5 to 30.5 days), Chinese (18 days; range, 2.8 to 90 days), and French (23 days; range, 3 to 47 days) groups. The complexity of these cases and the small number of patients in each series limit the validity of any strong conclusions, as many variables may explain the differences. Nevertheless, the patients treated with the VDR who survived ECMO for H1N1 pneumonia in the autumn of 2009 required fewer days to recover lung function than the patients in the ELSO registry, none of whom received VDR ventilation while on ECMO.

Retrospective comparisons of treatment by different providers in different centers are fraught with limitations. This study is somewhat unusual in that the patients were remarkably similar; all had ARDS from the H1N1 virus, and all were treated within a short period of time. The ELSO H1N1 registry provides a large data set with which to compare both processes and outcomes for a homogenous population with different treatment protocols. It is possible that factors other than the choice of ventilator for patients on ECMO differ between patients treated at LEH and the ELSO cohort, but the only differences apparent in the registry are the choice of ventilator management and the time these patients were on ECMO.

With regard to cost/benefit and risk/benefit evaluations of the value of ECMO for adult ARDS, the debates are fueled by both difficult analyses and emotion. The benefit side of the equation has been in constant controversy since the 1970s. Many observational series and randomized controlled trials, especially in the era of modern technologies and techniques, are demonstrating a clinical role for ECMO in the treatment of refractory hypoxemic ARDS. The most significant ECMO-associated risks as reported by ELSO are for bleeding and cerebral injury. Any strategy that reduces the time a patient must be anticoagulated would be expected to reduce these risks. The cost analyses are varied because of population and practice differences but are similar in their conclusions that ECMO adds only a modest cost to the care of severely compromised young patients who have the potential to recover many years of productive life without disability. The implication of our observation that the VDR may reduce the time necessary to recover from profound H1N1 ARDS in adults requiring ECMO has the potential to favorably affect both the risk/benefit and cost/benefit ratios by simply decreasing the left side of the equation. To determine if this strategy has clinical benefit will require the application of
prospective studies in the lab and in the intensive care unit under rigorous protocol.

References


