The Impact of a Standardized Refractory Hypoxemia Protocol on Outcome of Subjects Receiving Venovenous Extracorporeal Membrane Oxygenation

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BACKGROUND: Current mechanical ventilation practice and the use of treatment adjuncts in patients requiring extracorporeal membrane oxygenation (ECMO) for refractory hypoxemia (RH) vary widely and their impact on outcomes remains unclear. In 2015, we implemented a standardized approach to protocolized ventilator settings and guide the escalation of adjunct therapies in patients with RH. This study aimed to investigate ICU mortality, its associated risk factors, and mechanical ventilation practice before and after the implementation of a standardized RH guideline in patients requiring venovenous ECMO (VV-ECMO). METHODS: This was a single-center, retrospective cohort study of patients undergoing VV-ECMO due to RH respiratory failure between January 2008 and March 2015 (before RH protocol implementation) and between April 2015 and October 2019 (after RH protocol implementation). RESULTS: A total of 103 subjects receiving VV-ECMO for RH were analyzed. After implementation of the RH protocol, more subjects received prone positioning (6.7% vs 23.3%, *P* = .02), and fewer received high-frequency oscillatory ventilation than before launching the RH protocol (0% vs 13.3%, *P* = .01). Plateau pressure was also lower before initiation of ECMO (*P* = .04) and at day 1 during ECMO (*P* = .045). Driving pressure was consistently lower at days 1, 2, and 3 after ECMO initiation: median 13.0 (interquartile range [IQR] 10.6–18.0) vs 16.0 (IQR 14.0–20.0) cm H_2O at day 1 (*P* = .003); 13.0 (IQR 11.0–15.9) vs 15.5 (IQR 12.0–20.0) cm H_2O at day 2 (*P* = .03); and 12.0 (IQR 10.0–14.5) vs 15.0 (IQR 12.0–19.0) cm H_2O at day 3 (*P* = .005). CONCLUSIONS: The implementation of a standardized RH guideline improved compliance with a lung-protective ventilation strategy and utilization of the prone position and was associated with lower driving pressure during the first 3 days after ECMO initiation in subjects with refractory hypoxemia. *Key words: acute hypoxemic respiratory failure; refractory hypoxemia; mechanical ventilation; venovenous; extracorporeal membrane oxygenation; outcomes.* [Respir Care 2021;66(5):837–844.

Introduction

Patients with respiratory failure due to refractory hypoxemia (RH) are highly susceptible to ventilator-induced lung injury due to exposure to excessive mechanical stress and strain, which has been shown to be associated with significantly increased morbidity and mortality.[1-3] Once a patient's respiratory status or oxygenation remains unresponsive to conventional lung-protective ventilation strategy (ie, refractory hypoxemia), physicians may consider a number of adjunctive therapies to alleviate hypoxemia (eg, prone positioning, neuromuscular blockade, inhaled nitric oxide, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation [ECMO]). Current

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evidence supports the efficacy of early application of paralysis, prone positioning, and ECMO.[3-7] However, lack of a formal consensus statement or guideline regarding the stepwise implementation of effective adjunctive strategies to manage severe hypoxemia has led to wide variation in the use of these strategies, largely dependent on individual clinician expertise, equipment availability, or other nonclinical factors and limitations.[7-9]

Additionally, venovenous ECMO (VV-ECMO) is increasingly used in these patients, but little is known about ventilation strategy before and during VV-ECMO.[10] Theoretically, VV-ECMO provides adequate gas exchange, allowing a reduction in the intensity of ventilator support to enhance lung protection and decrease the risk of ventilator-induced lung injury.[11,12] To date, viewpoints based on expert opinion vary: some guidelines suggest a lung-rest strategy with minimal mechanical ventilation settings, thus requiring minimal alveolar recruitment, to avoid alveolar over-distention, which possibly favors atelectasis; another view suggests modest ventilator settings with high PEEP above the critical opening pressure and the smallest tidal volume that enables maximal alveolar recruitment with minimum driving pressure to promote lung healing and repair while mitigating the risk of over-distention.[13-17] Mechanical ventilation practices during VV-ECMO mainly depend on clinician's experience,[1] with wide ranging values for PEEP and tidal volume.[7,8] Delay between intubation to initiation of ECMO and any injurious ventilation before, during, and after ECMO may be associated with worse outcomes.[18-22] The use of adjunct therapies, optimal ventilator settings, and how to balance these while minimizing ventilator-induced lung injury and maximizing healing of the injured lung in patients requiring ECMO for refractory hypoxemia remain uncertain.[1,13-16]

In 2015, our institution developed and implemented a protocolized, stepwise approach to mechanical ventilation with clearly defined thresholds and a time line for management changes in RH.[23] We hypothesized that the rapid delivery of a safe and protocolized ventilation strategy for most patients, as well as timely identification of patients with RH, would allow for the appropriate implementation of adjunctive interventions, and that earlier escalation to ECMO when indicated may improve adherence with a lung-protective ventilation strategy and ICU mortality. This study aimed to investigate ICU mortality, its associated risk factors, and mechanical ventilation practice before and after implementation of our institution's RH protocol in patients who required VV-ECMO for RH.

QUICK LOOK

Current knowledge

Current mechanical ventilation practice and the use of treatment adjuncts in patients requiring extracorporeal membrane oxygenation (ECMO) for refractory hypoxemia vary widely, and their impact on outcomes remains unclear. In addition, the impact of a standardized protocol for refractory hypoxemia on mechanical ventilation practice and outcomes of patients requiring venovenous ECMO remains unknown.

What this paper contributes to our knowledge

The implementation of a standardized protocol to treat refractory hypoxemia improved compliance with a lung-protective ventilatory strategy and increased the utilization of the prone position, The protocol was associated with lower driving pressure during the first 3 d after initiation of ECMO in subjects with refractory hypoxemia.

Methods

Study Design and Subjects

This was a single-center, retrospective cohort study. All consecutive adult patients receiving VV-ECMO for > 24 h due to refractory hypoxemic respiratory failure in the ICU of the Mayo Clinic in Rochester, Minnesota, from January 1, 2008, through October 1, 2019, were included. Patients < 18 y old, in moribund state, or only receiving palliative care when admitted to the ICU were excluded. Patients who denied access to their medical records for research purposes were not included in this study. The Mayo Clinic Institutional Review Board approved this study. The primary outcome of interest was ICU mortality. Key secondary outcomes of interest were mechanical ventilation practices while on ECMO, ECMO duration, and length of stay in the ICU and in the hospital.

Management of Mechanical Ventilation and ECMO

Our institution convened a multidisciplinary working group composed of critical care physicians, ECMO consultants, respiratory therapists, clinical nurse specialists, and other key stakeholders to develop a treatment protocol for

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Supplementary material related to this paper is available at http://www.rcjournal.com.

This study was supported by the Critical Care Research Committee of the Mayo Clinic, Rochester, Minnesota. The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.08584

RH that is based on the available evidence for optimizing ventilator settings and appropriate application of adjunctive strategies; this protocol was approved in March 2015.[23] Subjects were classified as either pre-RH protocol implementation (ie, those who received VV-ECMO for RH from January 2008 to March 2015) or post-RH protocol implementation (ie, those who received VV-ECMO for RH from April 2015 to October 2019). From January 2008 to March 2015, patients were treated with the conventional low tidal volume strategy (ie, 6 mL/kg predicted body weight, PEEP adjusted according to the F_{IO_2}/PEEP ARDSNet table, plateau pressure limited to 30 cm H_2O), and adjunctive therapies were managed at the discretion of the ICU team. The initiation of ECMO was decided jointly by treating ICU physicians and ECMO consultants.

From April 2015 to October 2019, all patients were managed with the RH protocol (see the supplementary materials at http://www.rcjournal.com). This RH protocol provided a timely, evidence-based, best-practice guideline for mechanical ventilation and for the identification and management of RH with a stepwise escalation to adjunctive strategies at predetermined timelines.

Refractory hypoxemia was defined as $S_{pO_2} < 92\%$ with $F_{IO_2} \geq 0.60$ and failure to increase S_{pO_2} by 5% or compliance by 10% with a recruitment maneuver. Once RH was identified, higher PEEP $\geq$ 15 cm H_2O was attempted, and consideration of esophageal manometry guidance and a trial of prone position were to be initiated within 6 h. If a subject was hemodynamically unstable or had no response to those treatments, ECMO candidacy would be considered while initiating alternative strategies. The decision to initiate ECMO was made by treating ICU physicians and ECMO consultants.

Data Collection

We retrospectively reviewed the electronic medical records of all eligible patients and extracted their relevant demographic and clinical data before and during the VV-ECMO run. Demographic data included gender, height, weight, Acute Physiology and Chronic Health Evaluation (APACHE) III score at admission to ICU, and chronic comorbidities. We also extracted reasons for refractory hypoxemic respiratory failure (ie, pneumonia, non-pneumonia); adjunctive therapies (ie, nitric oxide, prone positioning, high-frequency oscillatory ventilation, neuromuscular blockade before ECMO, intervals between ICU admission or start of mechanical ventilation and ECMO initiation); ventilator settings (ie, tidal volume per predicted body weight, plateau pressure [P_{plat}], driving pressure [defined as the difference between P_{plat} and PEEP], PEEP, F_{IO_2}, minute ventilation prior to ECMO and every 15 min on days 1, 2, 3, and 7 during ECMO); ECMO settings (ie, cardiac index, circuit flow every hour on days 1, 2, 3, and 7 during ECMO); P_{aO_2} and lactate if available prior to ECMO; and outcomes (ie, ECMO support time, duration of mechanical ventilation, ICU and hospital mortality, ICU and hospital length of stay).

Statistical Analysis

Subject characteristics among the cohort are described using *n* (%), median (interquartile range), or mean ± SD. Simple comparisons between continuous variables were made with Wilcoxon rank sum tests, and comparisons between categorical variables were made with Pearson chi-square tests. Multivariable hazard ratios were calculated using proportional hazard regression analyses. To minimize bias, qualification on the evolution of the subject during ECMO stay was done by analyzing de-identified plots of the changes of each variable in time (see the supplementary materials at http://www.rcjournal.com). All VV-ECMO patients after implementation of the refractory hypoxemia protocol were included, and the timeframe for inclusion of VV-ECMO patients was limited to 2008 and after to control for possible confounding from changes in mechanical ventilation and ICU practices, which inevitably occur over time. Due to sample size constraints, the number of variables included in the multivariable analysis was limited, and variables included were chosen a priori on the basis of physiologic plausibility.

Results

Baseline Characteristics

During the study period, 105 patients received VV-ECMO for respiratory failure due to refractory hypoxemia; of these patients, 2 were excluded due to denying access to their medical records. A total of 103 subjects were analyzed, including 60 subjects who were treated before implementation of the RH protocol (pre-RH protocol) and 43 subjects after the implementation of RH protocol (post-RH protocol). Subject characteristics are showed in Table 1. Pneumonia was the main etiology for respiratory failure due to RH (ie, 52.4% of subjects had pneumonia as the main cause of RH).

Ventilator Settings and Adjunctive Therapies Prior to ECMO

Ventilator settings and the use of adjunctive therapies prior to ECMO before and after the implementation of RH protocol are presented in Table 1. After the implementation of the RH protocol, the median (IQR) interval from the start of mechanical ventilation to start of ECMO decreased from 10.7 (1.4–96.0) h to 4.0 (0.0–51.9) h ($P = .08$). After implementation of the RH protocol, median (IQR) P_{plat} prior to ECMO initiation decreased from 33.0 (29.5–37.0) cm H_2O to 29.0

Table 1. Subject Data

	After Protocol ($n = 43$)	Before Protocol ($n = 60$)	Total ($N = 103$)	P
Age, y	50.3 ± 17.3	44.4 ± 15.7	46.9 ± 16.6	.07
Female	13 (30.2)	29 (48.3)	42 (40.8)	.07
Body mass index, kg/m^2	29.7 ± 7.2	30.8 ± 7.7	30.3 ± 7.5	.56
APACHE III score at day 1 in the ICU	8.0 (6.0–117.0)	78.5 (58.5–104.0)	79.0 (6.0–106.0)	.49
Pneumonia as reason for RH	25 (58.1)	29 (48.3)	54 (52.4)	.33
Comorbidities				
Chronic heart disease	15 (34.9)	22 (36.7)	37 (35.9)	.85
Chronic lung disease	13 (30.2)	14 (23.3)	27 (26.2)	.43
Chronic liver disease	0 (0)	1 (1.7)	1 (1.0)	.39
Chronic kidney disease	4 (9.3)	4 (6.7)	8 (7.8)	.62
Time from ICU admission to ECMO start, h	26.5 (0.0–115.7)	17.4 (2.7–155.2)	22.8 (1.1–118.5)	.67
Time from start of mechanical ventilation to ECMO start, h	4.0 (0.0–51.9)	10.7 (1.4–96.0)	9.9 (0.0–63.5)	.08
Ventilator settings before ECMO				
Plateau pressure, cm H_2O	29.0 (28.0–33.0)	33.0 (29.5–37.0)	31.0 (29.0–35.0)	.04
Subjects, n	17	28	45	
Driving pressure, cm H_2O	17.0 (14.5–21.0)	20.5 (16.0–26.0)	18.5 (15.1–25.0)	.09
Subjects, n	24	40	64	
Tidal volume per PBW	6.0 (5.2–7.0)	6.1 (5.3–7.2)	6.1 (5.3–7.1)	.79
Subjects, n	26	40	66	
PEEP, cm H_2O	10.5 (8.0–14.5)	12.0 (8.0–15.0)	12.0 (8.0–15.0)	.51
Subjects, n	24	40	64	
F_{IO_2}	100 (86.3–100)	100 (87.5–100)	100 (90–100)	.79
Subjects, n	26	41	67	
Expiratory minute volume, L/min	8.5 (7.1–11.1)	10.6 (6.7–13.8)	10.2 (7.0–12.6)	.17
Subjects, n	25	37	62	
P_{aO_2}/F_{IO_2}	68.0 (54.0–94.0)	55.0 (45.0–73.0)	59.0 (47.0–79.0)	.07
Subjects, n	35	56	91	
Lactate, mmol/L	2.3 (1.2–5.5)	3.4 (1.5–6.3)	3.0 (1.5–6.2)	.27
Subjects, n	28	54	82	
Adjunctive therapies prior to ECMO				
Prone positioning	10 (23.3)	4 (6.7)	14 (13.6)	.02
Nitric oxide	7 (16.3)	10 (16.7)	17 (16.5)	.96
Paralysis	15 (34.9)	22 (36.7)	37 (35.9)	.85
High-frequency oscillatory ventilation	0 (0)	8 (13.3)	8 (7.8)	.01

Data are presented as n (%), median (interquartile range), or mean ± SD. Simple comparisons between continuous variables were done using Wilcoxon rank sum tests, and comparisons between categorical variables were done using Pearson chi-square tests.
ECMO = extracorporeal membrane oxygenation
RH = refractory hypoxemia
PBW = predicted body weight

(28.0–33.0) cm H_2O ($P = .04$), and the median (IQR) driving pressure decreased from 20.5 (16.0–26.0) to 17.0 (14.5–21.0) cm H_2O ($P = .09$). There were no significant differences in the interval from ICU admission to start of ECMO, tidal volume per predicted body weight, PEEP, P_{aO_2}/F_{IO_2}, and lactate after implementation of the RH protocol.

More subjects received prone positioning after the implementation of RH protocol than before the RH protocol (23.3% vs 6.7%, $P = .02$), and high-frequency oscillatory ventilation was no longer used after the implementation of RH protocol (0% vs 13.3%, $P = .01$). There was no significant difference in the use of nitric oxide (16.3% vs 16.7%, $P = .85$) and paralysis (34.9% vs 36.7%, $P = .96$).

Outcomes and Risk Factors Associated With ICU Mortality

The overall ICU mortality rate was 45.6% (47 of 103 subjects); 51.7% of subjects before implementation of the RH protocol and 37.2% of subjects after implementation of RH protocol died during the ICU stay (Table 2). Kaplan-Meier survival estimates for subjects receiving VV-ECMO for respiratory failure due to RH revealed a 14.5% difference in ICU mortality rate between the 2 periods before and after the implementation of RH protocol, although this finding did not reach statistical significance ($P = .14$) (Fig. 1). Ventilator-free days over the 28-d monitoring

Table 2. Outcomes

	After Protocol ($n = 43$)	Before Protocol ($n = 60$)	Total ($N = 103$)	P
Duration of mechanical ventilation, d	18.2 (10.4–30.7)	22.8 (10.6–30.9)	20.7 (10.5–30.7)	
Ventilator-free days	0.0 (0.0–11.4)	0.0 (0.0–2.6)	0.0 (0.0–7.3)	
Duration of ECMO, d	10.1 (4.9–16.4)	12.8 (5.0–20.9)	10.2 (5.0–19.0)	
ICU length of stay, d	26.6 (11.6–39.0)	25.4 (12.1–39.2)	25.8 (12.0–39.0)	
Hospital length of stay, d	34.5 (14.4–48.9)	29.8 (18.6–47.5)	30.8 (16.8–48.5)	
ICU mortality	16 (37.2)	31 (51.7)	47 (45.6)	.14

Data are presented as median (interquartile range) or *n* (%). Simple comparisons between continuous variables were done using Wilcoxon rank sum tests. ICU mortality was analyzed with the log-rank test.
ECMO = extracorporeal membrane oxygenation

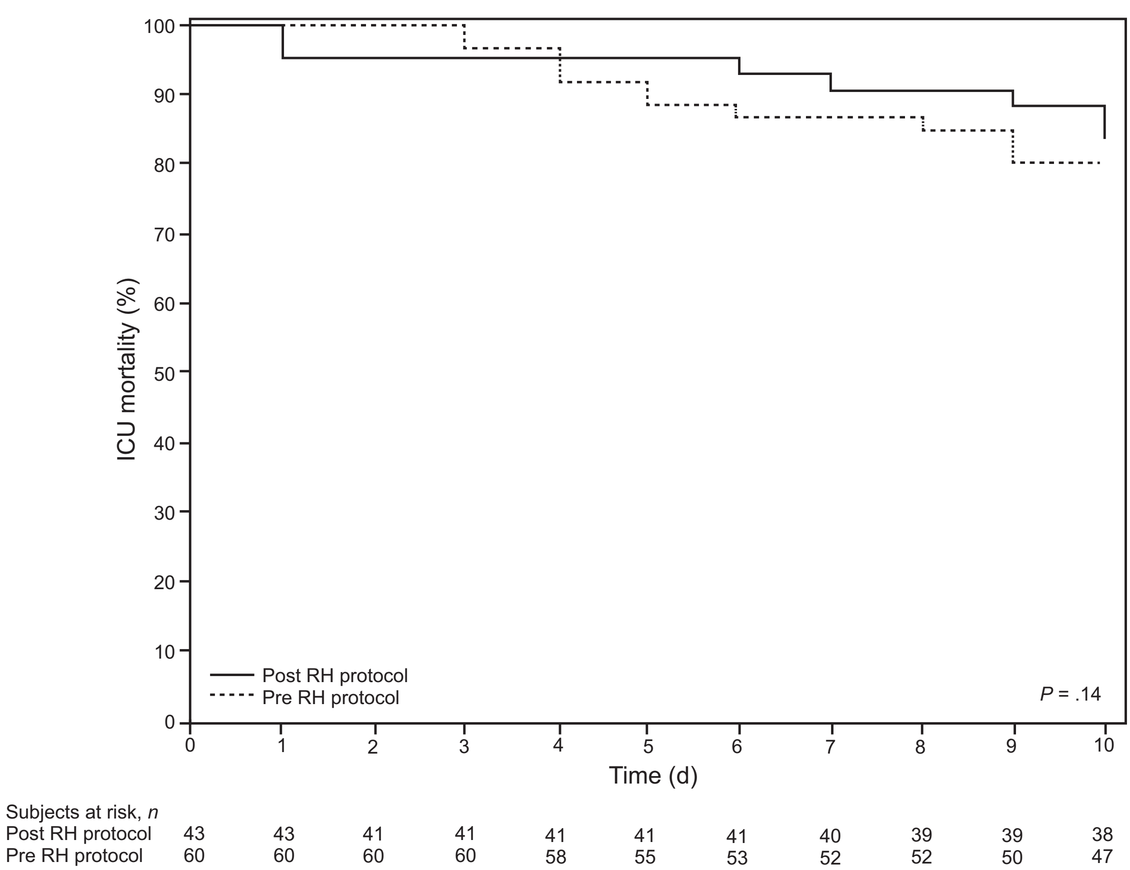

Fig. 1. ICU survival between periods before and after the implementation of refractory hypoxemia (RH) protocol.

period and the median duration of mechanical ventilation, ECMO duration, ICU length of stay, and hospital length of stay were all similar between the 2 periods (Table 2).

Risk factors associated with ICU mortality were assessed using a multivariable proportional hazard regression model. After the multivariable adjustment, age was associated with increased risk of ICU mortality (hazard ratio 1.027, 95% CI 1.007–1.047, $P = .008$) (Table 3).

Mechanical Ventilation Management After ECMO

Mechanical ventilation and ECMO settings were recorded every 15 min, and we analyzed the mean of these data on days 1, 2, 3, and 7 after ECMO initiation. In comparison with ventilator settings prior to ECMO (tidal volume, P_{plat}, driving pressure, minute ventilation, and F_{IO_2} were significantly reduced after initiation of ECMO support both before

Table 3. Multivariable Hazard Ratios of ICU Death From ECMO Start Date

	Hazard Ratio (95% CI)	*P*
After vs. before protocol	0.576 (0.301–1.102)	.10
Body mass index	1.023 (0.981–1.067)	.29
APACHE III score at day 1	0.999 (0.990–1.008)	.82
Pneumonia as reason, yes vs no	0.556 (0.307–1.008)	.053
Age	1.027 (1.007–1.047)	.008

ECMO = extracorporeal membrane oxygenation
APACHE III = Acute Physiology and Chronic Health Evaluation III

and after implementation of the RH protocol ($P < .05$). PEEP levels were relatively maintained after implementation of the RH protocol, but they were reduced during the period before launching the RH protocol ($P < .05$) (see the supplementary materials at http://www.rcjournal.com).

After ECMO initiation, compared with the ventilator settings during the period before the RH protocol, median (IQR) P_{plat} was decreased at day 1 [23.5 (19.0–28.0) vs 25.0 (22.0–29.0) cm H_2O, $P = .045$], median (IQR) driving pressure was consistently lower at days 1, 2, and 3 [13.0 (10.6–18.0) vs 16.0 (14.0–20.0) cm H_2O, $P = .003$; 13.0 (11.0–15.9) vs 15.5 (12.0–20.0) cm H_2O, $P = .03$; 12.0 (10.0–14.5) vs 15.0 (12.0–19.0) cm H_2O, $P = .005$, respectively]. Median (IQR) PEEP values on ECMO days 1, 2, 3, and 7 during the period before and after RH protocol implementation were 9.7 (5.7–11.2) vs 9.9 (8.0–11.9) cm H_2O ($P = .29$); 10 (7.1–10.0) vs 10.6 (8.0–15.9) cm H_2O ($P = .07$); 10 (7.5–10.9) vs 10 (8.0–12.4) cm H_2O ($P = .26$); and 10 (8.0–12.0) vs 11.9 (9.9–14.7) cm H_2O ($P = .04$), respectively. There was no significant difference in other ventilator settings such as tidal volume, minute ventilation, F_{IO_2}, ECMO settings, ECMO cardiac index, and circuit flow during the 2 periods (ie, before and after implementation of the RH protocol).

Discussion

Mechanical ventilation practice during ECMO has been reported in several previous studies.[15-22] To our knowledge, this is the first study to examine the use of an evidence-based protocol for the management of refractory hypoxemia before the initiation of VV-ECMO and to determine its effect on mortality. There has been widespread adoption of lung-protective ventilation strategy for hypoxemic respiratory failure, but it may not suffice for patients with RH.[8] Current evidence supports the efficacy of early use of adjuncts in treating RH, including paralysis and prone positioning.[3-7] Due to life-threatening consequences, RH presents a compelling case for clinicians to consider the use of adjuncts. To date, many institutions have no formal protocol to guide the identification or management of RH, and thus the use and practice of adjunctive therapies varies widely.[8] Our institution developed an evidence-based, best-practice mechanical ventilation guideline for RH, with the aim to address the correct identification of patients with true refractory hypoxemia, to rule out reversible causes, to personalize ventilator settings, and to guide stepwise escalation to rescue and adjunct therapies in a timely fashion. The study presented here is consistent with and complementary to our colleagues' recent study, which reported that the RH protocol led to earlier identification of subjects with true RH and a shorter time to initiation of prone positioning.[23] The study presented here examined in detail the subpopulation of patients with RH who progressed to the point of requiring ECMO, and the potential effects of the RH protocol on their care and outcomes.

There were 3 main findings of the present study. First, the implementation of the RH protocol was associated with more frequent use of prone ventilation, lower P_{plat} prior to ECMO initiation and on day 1 on ECMO, and consistently lower driving pressure at days 1, 2, and 3 after initiation of ECMO. Second, ECMO support promoted the use of lung-protective ventilation, and ventilator settings were reduced significantly during ECMO in both cohorts (ie, before and after implementation of the RH protocol). Third, the ICU mortality rate decreased by 14.5% after the RH protocol, although this association between RH protocol and ICU mortality did not reach statistical significance and should be considered a hypothesis-generating result. Possible explanations for this potential effect on ICU mortality is that the implementation of the RH protocol facilitated the use of lung-protective ventilation strategies before and during ECMO. More specifically, our study indicates that the implementation of the RH protocol was associated with more frequent use of prone positioning, lower P_{plat} prior to ECMO and on day 1 after initiation of ECMO, and the mean driving pressure was consistently lower on days 1, 2, and 3 after initiation of ECMO (all $P < .05$). Thus, mechanical ventilation before and during ECMO may have an important impact on mortality. We did not analyze the association between discrete ventilator settings and outcome, as this study was not designed to specifically test that hypothesis.

The evidence base for lung-protective ventilation in ARDS (including prone positioning, P_{plat} limitation, and driving pressure) may provide insights as to why the changes in management that we observed after implementation of the RH protocol could theoretically improve the outcomes of patients on ECMO. Prone positioning may help prevent ventilator-induced lung injury by homogenizing the distribution of stress and strain within lungs, improve oxygenation and airway drainage, thus improve outcome.[4,24] Absence of prone position before ECMO has been independently associated with 6-month mortality.[25]

The increase in the use of prone positioning after implementation of the RH protocol is a potential explanation for the trend toward a decrease in ICU mortality seen in our study. It is worth noting that there was likely still room to increase the use of this relatively simple, inexpensive, and proven intervention in our cohort.

Retrospective studies have reported that $P_{plat} > 30$ cm H_2O prior to ECMO was an independent predictor of ICU mortality.[20,25] Our results indicate that the mean P_{plat} prior to ECMO before launching our RH protocol was 34.0 cm H_2O, which is above the recommended lung-protective level. In our study, the mean P_{plat} prior to initiation of ECMO decreased to 29.5 cm H_2O after implementation of the RH protocol, which is within the lung-protective range and consequently may have reduced the risk of ventilator-induced lung injury.

As in patients with ARDS who are not treated with ECMO, increased driving pressure during ECMO has consistently been reported as an independent risk factor for mortality in patients receiving ECMO for refractory hypoxemia.[19,26-28] In our study, driving pressure during the first 3 d of ECMO was consistently lower after implementation of the RH protocol than driving pressure in the cohort treated prior to the launch of our RH protocol. This may be another potential contributor to the observed trend toward lower ICU mortality after the implementation of our RH protocol.

Finally, although ECMO facilitates a reduction in the intensity of mechanical ventilation while maintaining adequate gas exchange, optimal targets for ventilator settings remain unclear. Consistent with previous studies, tidal volume, P_{plat}, driving pressure, and F_{IO_2} were all significantly decreased after initiation of ECMO in both study cohorts (ie, before and after RH protocol implementation).[22,26] However, PEEP levels during ECMO were generally higher after implementation of the RH protocol. After RH protocol implementation, the mean tidal volume, P_{plat}, PEEP, and driving pressure at day 1 during ECMO were 4.4 mL/kg predicted body weight, 23.5 cm H_2O, 10.3 cm H_2O, and 14.1 cm H_2O, respectively, and these values are consistent with the concept of ultraprotective ventilation.[29,30]

A strength of our study is our robust electronic database, which captured data on key aspects of mechanical ventilation and ECMO at least every 15 min during our study period. On the other hand, our study has several limitations. First, this was a single-center, before-and-after (historical cohort) retrospective design. Due to the relatively infrequent use of ECMO, although we included all patients who required VV-ECMO for refractory hypoxemia since January 2008, when the low tidal volume ventilation protocol at bedside was launched, the sample size in our study was limited. The negative results of the OSCILLATE and OSCAR trials, and the positive results of PROSEVA trial, were all published in 2013,[24,32] and these data and the subsequent choice of adjunct therapies are potential confounders in our study. Finally, we did not analyze the relationships between mortality and individual variables of ventilator settings and specific adjunctive treatments, as statistical power for such analyses was expected to be prohibitively low.

Conclusions

The implementation of a standardized refractory hypoxemia guideline improved adherence with a lung-protective ventilatory strategy and utilization of prone positioning before ECMO, and it was associated with lower driving pressure on ECMO days 1, 2, and 3 in subjects with RH requiring ECMO. Our data suggest that the implementation of a standardized RH guideline may have an impact on ICU mortality in patients requiring VV-ECMO to treat RH. However, further research is required to better determine the effect of mechanical ventilation strategies before and during ECMO on mortality and other important patient outcomes.

ACKNOWLEDGMENTS

We thank Lei Fan, IT Analyst/Programmer in the Department of Information Technology, and Grant D Wilson, respiratory therapist in the Department of Respiratory Therapy, at the Mayo Clinic for their help with this study.

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