ORIGINAL CLINICAL REPORT

OPEN

# Physiologic Improvement in Respiratory Acidosis Using Extracorporeal $Co_2$ Removal With Hemolung Respiratory Assist System in the Management of Severe Respiratory Failure From Coronavirus Disease 2019

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**OBJECTIVES:** About 15% of hospitalized coronavirus disease 2019 patients require ICU admission, and most (80%) of these require invasive mechanical ventilation. Lung-protective ventilation in coronavirus disease 2019 acute respiratory failure may result in severe respiratory acidosis without significant hypoxemia. Low-flow extracorporeal $Co_2$ removal can facilitate lung-protective ventilation and avoid the adverse effects of severe respiratory acidosis. The objective was to evaluate the efficacy of extracorporeal $Co_2$ removal using the Hemolung Respiratory Assist System in correcting severe respiratory acidosis in mechanically ventilated coronavirus disease 2019 patients with severe acute respiratory failure.

**DESIGN:** Retrospective cohort analysis of patients with coronavirus disease 2019 mechanically ventilated with severe hypercapnia and respiratory acidosis and treated with low-flow extracorporeal $Co_2$ removal.

**SETTING:** Eight tertiary ICUs in the United States.

**PATIENTS:** Adult patients supported with the Hemolung Respiratory Assist System from March 1, to September 30, 2020.

**INTERVENTIONS:** Extracorporeal $Co_2$ removal with Hemolung Respiratory Assist System under a Food and Drug Administration emergency use authorization for coronavirus disease 2019.

**MEASUREMENTS AND MAIN RESULTS:** The primary outcome was improvement in pH and $Paco_2$ from baseline. Secondary outcomes included survival to decannulation, mortality, time on ventilator, and adverse events. Thirty-one patients were treated with Hemolung Respiratory Assist System with significant improvement in pH and $Pco_2$ in this cohort. Two patients experienced complications that prevented treatment. Of the 29 treated patients, 58% survived to 48 hours post treatment and 38% to hospital discharge. No difference in age or comorbidities were noted between survivors and nonsurvivors. There was significant improvement in pH (7.24 ± 0.12 to 7.35 ± 0.07; $p < 0.0001$) and $Paco_2$ (79 ± 23 to 58 ± 14; $p < 0.0001$) from baseline to 24 hours.

**CONCLUSIONS:** In this retrospective case series of 29 patients, we have demonstrated efficacy of extracorporeal $Co_2$ removal using the Hemolung Respiratory Assist System to improve respiratory acidosis in patients with severe hypercapnic respiratory failure due to coronavirus disease 2019.



**DOI: 10.1097/CCE.0000000000000372**

**KEY WORDS:** acute respiratory distress syndrome; acute respiratory failure; blood gas analysis; coronavirus disease 2019; extracorporeal carbon dioxide removal

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to severe acute respiratory failure that requires ICU admission in about 15 % of hospitalized patients (1). Most (80%) patients admitted to an ICU require invasive mechanical ventilation. The reported mortality in patients requiring invasive mechanical ventilation ranges from 53% to 88% (1, 2). The management of mechanical ventilation in patients with COVID-19 respiratory failure is evolving. From recently published data, it appears that the respiratory mechanics of COVID-19 acute respiratory distress syndrome (ARDS) could be like non–COVID-19 ARDS with current recommendations that support the use of low tidal volume ventilation in mechanically ventilated COVID-19 ARDS patients (3). Lung-protective ventilation (LPV) with low tidal volumes has been proven to reduce mortality in patients with ARDS (4). When such LPV and other therapies such as prone positioning are not sufficient to support these patients, newer technologies have been gaining momentum. Venovenous extracorporeal membrane oxygenation (VV ECMO) is a form of extracorporeal life support that provides support of gas exchange, including both oxygenation and $Co_2$ removal. In cases of severe hypoxemia, it allows for full support of oxygenation. The efficacy of this therapy as a rescue modality has been examined in an exponentially rising number of studies since 2000, and survival rates are increasing (5). There are several known risks with this modality, which are divided into patient related or circuit related adverse events. These include hemorrhage, extremity ischemia, pump failure, oxygenator failure, and thrombus formation (5).

Some patients receiving low tidal volume ventilation develop severe respiratory (hypercapnic) acidosis despite adequate oxygenation. Severe hypercapnia and hypercapnic acidosis have been shown to be independently associated with increased adverse effects, including increased ICU and hospital mortality, in mechanically ventilated patients (6–8). There is no precedent for the widespread initiation of extracorporeal $CO_2$ removal during a pandemic. Extracorporeal $Co_2$ removal ($ECCO_2R$) as a technology is relatively new, and it has not been substantially used in previous pandemics. $ECCO_2R$ is less resource intensive than VV ECMO and may be a viable alternative for therapy when hypoxemia is not severe (9–11). An $ECCO_2R$ device called the Hemolung Respiratory Assist System (RAS) (ALung Technologies, Pittsburgh, PA) is currently available for use in the United States under a temporary Food and Drug Administration (FDA) emergency use authorization (EUA) for the SARS-CoV-2 pandemic to manage severe hypercapnia that may be associated with low tidal volume ventilation in COVID-19 ARDS patients. Such devices are shown to facilitate LPV while avoiding severe hypercapnia (9). Here, we present the experience of eight centers who used this therapy in 31 patients with COVID-19. We describe patient demographics, outcomes, and suggestions for further incorporation inpatient care. The aim of this study is to assess the physiologic efficacy and safety of using the Hemolung RAS in mechanically ventilated COVID-19 ARDS patients with severe hypercapnia.

## METHODS

This retrospective, multicenter study was conducted from cases of patients placed on Hemolung RAS at eight sites across the USA. Deidentified data from patients treated between March 4, and September 30, 2020 with known discharge status were obtained retrospectively from the Hemolung RAS device registry maintained as part of the FDA EUA reporting requirements. This registry maintains safety, patient, and device performance data. The Institutional Review Board at each center was notified of the use of the device and the reporting of data to the registry with each occurrence per the FDA EUA requirements.

### Intervention

The Hemolung RAS was supplied by the manufacturer under conditions of the FDA EUA, and training was provided prior to use. The Hemolung RAS is a fully integrated three-component system consisting of a controller, a disposable gas exchange cartridge, and a 15.5F dual-lumen, central venous catheter. The cartridge is an integrated centrifugal pump and heparin-coated hollow fiber membrane blood gas exchanger. The Hemolung catheter is inserted percutaneously using

a standard Seldinger technique via either the internal jugular vein or the femoral vein. Therapy operates at blood flows of 350–550 mL/min and removes 30–50% of basal metabolic $Co_2$ production. The Hemolung RAS is not intended to provide therapeutic levels of oxygenation. Systemic anticoagulation is required during therapy and is recommended to be provided with unfractionated heparin to achieve an activated partial thromboplastin time in the range of 50—70 seconds. The FDA grants EUA to products that "may be effective" to prevent, diagnose, or treat in humans serious or life-threatening diseases or conditions that can be caused by the specified biological, chemical, radiological, or nuclear agent(s) that led to or caused a declared emergency. The "may be effective" standard for EUAs provides for a lower level of evidence than the "effectiveness" standard that FDA uses for product approvals. An EUA can also be granted when there is no alternative to the therapy, and as such the Hemolung device was granted an EUA.

### Statistical Analysis

Continuous variables are reported as mean ± SD or median (interquartile range). Samples were compared with the *t* test or Mann-Whitney *U* test as appropriate. Proportions were compared with the chi-square statistic or Fisher exact test. Physiologic measurement data were tested for normal distribution using the Kolmogorov-Smornov test. The ability of the Hemolung to correct hypercapnia and respiratory acidosis was evaluated by analyzing pH and $Paco_2$ from blood gas data, respiratory rate, tidal volume, and minute ventilation during the first 24 hours of Hemolung therapy. The overall 24-hour trend was analyzed with analysis of covariance. To better describe the trend, the data were then categorized into intervals of baseline, 0–4, 4–8, 8–16, and 16–24 hours post initiation and analyzed with a two-way general linear model using least-squares means and the Tukey-Kramer multiple comparison designed to handle unbalanced datasets.

## RESULTS

A total of 31 patients are included in this study. Two patients underwent cannulation but were never started on therapy due to a vascular access failure in one patient and immediate circuit clotting in the other. For 29 patients who received Hemolung treatment, analysis of covariance revealed a significant improvement trend in both pH and $Paco_2$ ($p < 0.0001$). Comparison of time intervals yielded a statistically significant improvement in pH (7.24 ± 0.12 to 7.35 ± 0.07; $p < 0.0001$) (**Fig. 1**) and decrease in $Pco_2$ (79 ± 23 to 58 ± 14; $p < 0.0001$) (**Fig. 2**) from baseline to 24 hours after start of therapy. There were numerical but not significant decreases from baseline to 24 hours in respiratory rate (26.6 ± 5.4 to 23.4 ± 4.9), tidal volume (407 ± 100 to 386 ± 75 mL), and minute ventilation (10.2 ± 3.2 to 8.7 ± 2.2 L/min).

Survival to 48 hours post decannulation was 58%, and survival to discharge was 38%. In a comparison of survivors with nonsurvivors (**Table 1**), there was no significant statistical difference in age (56.1 ± 11.5 vs 53.8 ± 12.1; 0.31), body mass index (33.7 ± 8.3 vs 33.5 ± 10.5; 0.48), prevalence of diabetes (27% vs 33%; 0.27), hypertension (36% vs 22%; 0.5), number of comorbidities (3.8 vs 5.6; 0.13), number of days from hospital admission to mechanical ventilation (8.0 vs 6.8; 0.38), or number of days from start of mechanical ventilation to use of Hemolung (17.3 vs 15.1; 0.34). Baseline $Pco_2$ and $Pao_2/Fio_2$ were statistically higher in survivors (93 vs 71.2 mm Hg; 0.03 and 176 vs 116 mm Hg; 0.046).

Average duration of Hemolung therapy was 14.1 days (median 10.8 d; range, 5–38 d) in survivors and 9.1 days (median 7.6 d, range 2–27 d) in nonsurvivors. Three of the 29 patients received more than two units of packed red blood cells during Hemolung therapy, and moderate hemolysis was reported in four patients.

## DISCUSSION

Evidence-based management of severe ARDS is heavily reliant on lung-protective ventilation (LPV). LPV limits tidal volumes to 6–8 mL/kg of predicted body weight or lower to improve survival (4, 12, 13). LPV minimizes ventilator-induced lung injury (VILI). VILI can result from four distinct mechanisms: volutrauma caused by alveolar overdistention, barotrauma caused by increased transpulmonary pressure, atelectotrauma caused by repetitive opening and closing of alveoli, and biotrauma leading to an increase in proinflammatory cytokines (13–15). In COVID-19, patients may have relatively preserved pulmonary compliance when compared with typical ARDS due to other pathologies but may still develop significant hypercapnia due to an increase in dead space ventilation fraction (16–21). Even

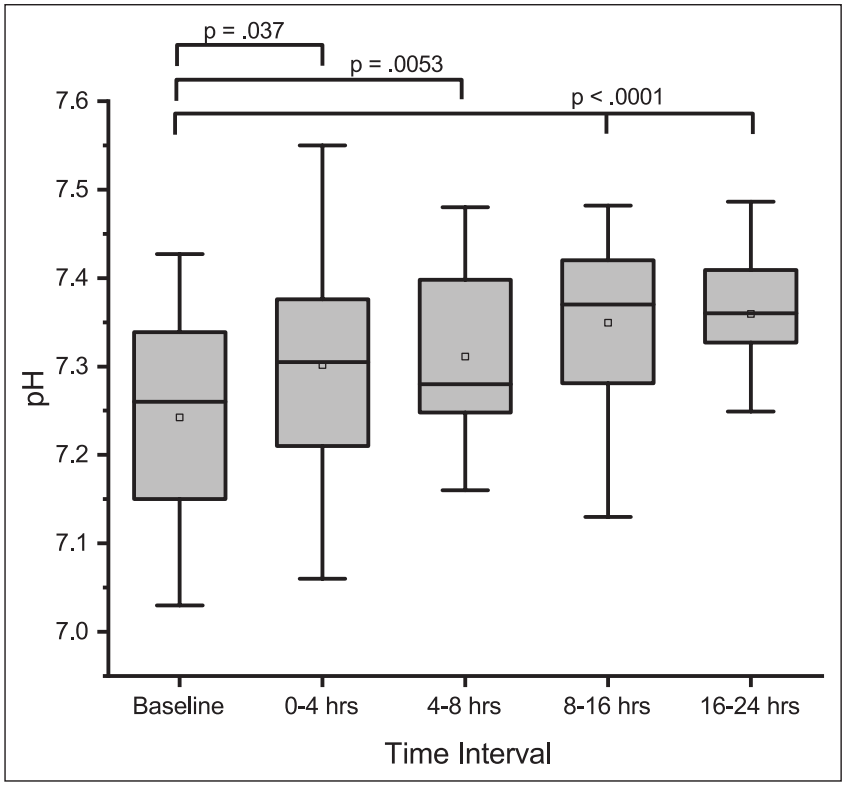


**Figure 1.** Boxplot depicting the baseline pH prior to cannulation and the improvement in pH over the first 24 hr.

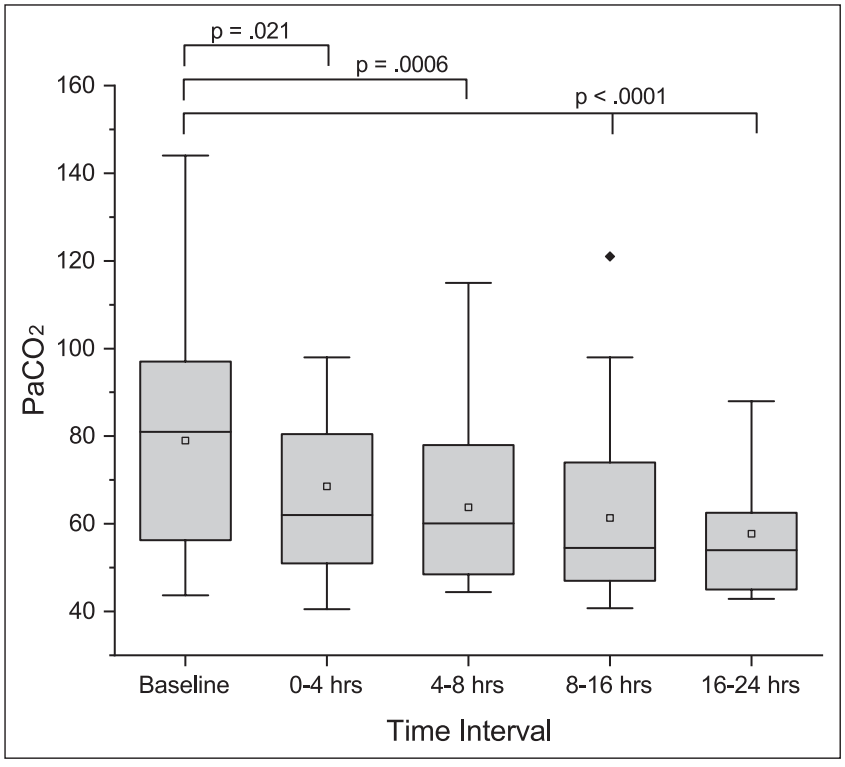


**Figure 2.** Boxplot depicting the baseline $Paco_2$ prior to cannulation and the improvement in $Paco_2$ over the first 24 hr.

though permissive hypercapnia has been lauded as effective therapy for ARDS for decades, this is a tolerated but not desirable sequelae while providing LPV. Severe hypercapnic respiratory failure leads to severe acidosis and can lead to poor outcomes (6, 7). Hypercapnia has several adverse effects including contributing to hypoxemia by decreasing the $Po_2$ in the alveoli, increasing intracranial and intraocular pressure, and increasing pulmonary artery pressure that can lead to right heart failure and cardiorenal syndrome. Hypercapnia also depresses myocardial function and cardiac output, which can lead to a decrease in the mixed venous saturation and worsened oxygen delivery. In patients with severe renal dysfunction, hypercapnia cannot be compensated for, which can lead to severe acidosis. In patients with sepsis, hypercapnia is particularly worrisome as it can lead to a significant decrease in the systemic vascular resistance. For these reasons, permissive hypercapnia is relatively contraindicated in patients with acute cerebral disease, patients with coronary artery disease, heart failure, cardiac arrhythmias, or pulmonary hypertension (22).

COVID-19 ARDS may coexist with or amplify COVID-19–related endothelial consequences of hypercoagulability and microthrombi as shown in multiple studies this year (23–26). Pulmonary microvascular injury and thrombosis are being reported as coexisting features of COVID-19 respiratory failure, and it is plausible that hypercapnic respiratory failure could be a direct insult of such microvascular injury and thereby contributing to hypercapnia and worsening oxygenation status. This further supports the use of $ECCO_2R$ in a certain subset of patients (17).

In our study, we noticed early significant improvement of pH and $Pco_2$ after

**TABLE 1.**
**Characteristics of the Patient Cohort**

| Characteristics | Total ($n = 29$) | Survivors ($n = 11$) | Nonsurvivors ($n = 18$) | $p$ |
|---|---|---|---|---|
| Demographics | | | | |
| Age (yr), mean ± SD | 54.7 ± 11.5 | 56.1 ± 11.5 | 53.8 ± 11.8 | 0.31 |
| Sex (male), *n* (%) | 18 (62) | 8 (78) | 10 (59) | 0.35 |
| Race, *n* (%) | | | | |
| White, non-Hispanic | 7 (24) | 4 (36) | 3 (17) | 0.22 |
| White, Hispanic | 13 (45) | 3 (27) | 10 (55) | 0.09 |
| African American | 5 (17) | 2 (18) | 3 (17) | 0.91 |
| Other | 4 (14) | 2 (18) | 2 (11) | 0.59 |
| Body mass index, kg/m$^2$, mean ± SD | 33.5 ± 10.5 | 33.7 ± 8.3 | 33.5 ± 10.5 | 0.48 |
| Number of comorbidities, mean ± SD | 5.6 ± 4.2 | 3.8 | 5.6 | 0.11 |
| Diabetes mellitus, *n* (%) | 9 (31) | 3 (27) | 6 (33) | 0.27 |
| Hypertension, *n* (%) | 8 (28) | 4 (36) | 4 (22) | 0.5 |
| History of transplant, *n* (%) | 2 (7) | 0 (0) | 2 (11) | 0.59 |
| Prone position at Hemolung initiation, % | 41 | 45 | 40 | 0.72 |
| Inhaled nitric oxide, *n* (%) | 5 (17) | 1 (9) | 4 (22) | 0.36 |
| Patients on ECMO prior to Hemolung, *n* (%) | 6 (21) | 4 (36) | 2 (10) | 0.10 |
| Days from admission to MV, mean ± SD | 7.3 ± 9.0 | 8 ± 8.7 | 6.8 ± 9.3 | 0.38 |
| Median days from admission to MV, median (interquartile range) | 4.5 (0–10.25) | 5.5 (0.75–11.25) | 4 (0–9.75) | |
| Days from MV to Hemolung initiation, mean ± SD | 15.9 ± 17.6 | 17.3 ± 17.3 | 15.1 ±18.2 | 0.34 |
| Median days from MV to Hemolung initiation, median (interquartile range) | 8.5 (4–22.5) | 10 (5.26–29.75) | 8 (2.25–17.75) | |
| Baseline variables[a], mean ± SD | | | | |
| $PaCO_2$, mm Hg | 79.6 ± 32.0 | 93 ± 40.2 | 71.2 ± 23.0 | 0.03 |
| pH | 7.251 ± 0.135 | 7.217 ± 0.140 | 7.273 ± 0.130 | 0.12 |
| $PaO_2/FIO_2$ ratio | 136 ± 87 | 176 ±108 | 116 ± 70 | 0.046 |
| Respiratory rate, min$^{-1}$ | 28.4 ± 5.0 | 29.2 ± 4.5 | 27.9 ± 5.4 | 0.26 |
| Tidal volume, mL | 415 ± 107 | 391.7 ± 95 | 431 ± 114 | 0.19 |
| Minute ventilation, L/min | 11.4 ± 3.5 | 11.4 ± 3.4 | 11.5 ± 3.7 | 0.47 |

(*Continued*)

**TABLE 1. (*Continued*).**
**Characteristics of the Patient Cohort**

| Characteristics | Total ($n = 29$) | Survivors ($n = 11$) | Nonsurvivors ($n = 18$) | $p$ |
|---|---|---|---|---|
| Support | | | | |
| Duration of Hemolung support, d, mean ± SD | 11.1 ± 8.0 | 14.1 ± 9.3 | 9.1 ± 6.6 | 0.045 |
| Median duration of Hemolung support, d, median (interquartile range) | 8.2 (5.3–16.0) | 10.8 (8.33–17.51) | 7.6 (4.6–13.1) | |
| Number transitioned to ECMO, *n* | 2 | 0 | 2 | 0.51 |
| Hospital LOS, d, mean ± SD | 50.9 ± 40.0 | 81.5 ± 52 | 35 ± 19 | 0.0014 |
| Median hospital LOS, d, median (interquartile range) | 47.5 (26.5–66.25) | 69 (52.25–80.25) | 31 (22.25–50.25) | |

ECMO = extracorporeal membrane oxygenation, LOS = length of stay, MV = mechanical ventilation.
[a]Values obtained at time of decision for Hemolung support, reported as mean ± SD.

device cannulation, with the maximal improvement at 24 hours suggesting the physiologic goals were met. There were no decreases in the level of mechanical ventilation, and these patients were already receiving protective lung ventilation. The low survival in this small cohort most likely reflects the disease burden related to COVID-19 in this cohort. There was no significant difference in demographics between the survivors and nonsurvivors in our cohort. Physiologic success was achieved in all patients as shown in the improvement in $Paco_2$ and pH. Those who survived had a higher $Paco_2/Fio_2$ ratio compared with those patients who did not survive despite both groups having moderate ARDS by Berlin criteria. Survival was comparable to expected survival with extracorporeal membrane oxygenation (ECMO), but this study is unable to ascertain whether this is a treatment or patient selection effect, highlighting the need for randomized trials. Despite transitioning from $ECCO_2R$ to ECMO, two patients died suggesting the trajectory of ARDS was likely severe in those patients.

Cause of death in nonsurvivors was like what we have experienced with current standard of care treatment for severely ill COVID-19 patients. A few of these patients died due to sepsis, multiple organ failure, and intracranial hemorrhage causes which have been reported in noncannulated COVID-19 patients as well. Although $ECCO_2R$ is potentially safer than VV ECMO due to its smaller cannula size, single vascular site, and low blood flow, this study was too small to establish a better safety profile, and further trials are needed to fully establish safety. Two patients did not complete initiation of $ECCO_2R$ due to complications. One was a 74-year-old with severe peripheral vascular disease who sustained a vascular injury during cannulation attempt resulting in failed cannulation. The contralateral side was successfully cannulated, and anticoagulation started, but the patient deteriorated immediately afterwards and went into cardiac arrest due to mediastinal hematoma and pericardial effusion. Although this complication occurred despite prior experience with the device, it underscores its invasive nature and the risk of cannulation. The second was a 51-year-old who was successfully cannulated, but anticoagulation was unable to be started and the circuit clotted during initiation. The patient died the same day from inability to provide adequate gas exchange through mechanical ventilation.

Availability of $ECCO_2R$ as an additional tool in the arsenal of treatment options for severe COVID-19 offers multiple advantages. Certain patients may not meet criteria for VV ECMO or may not be admitted to a facility with an extracorporeal life support program, but the availability, differences in usability, and differences in the risk profile of the Hemolung enable its effective use. Cannulation for $ECCO_2R$ requires only a dual lumen cannula similar in design to, but slightly larger than, a hemodialysis catheter. In contrast, VV ECMO requires two single lumen or a single bicaval dual lumen cannula to support blood flow

rates sufficient for oxygenation. The Extracorporeal Life Support Organization has guidelines that outline the institutional requirements for an ECMO program, and they are substantial. Establishing and maintaining a program is resource intensive, and trained staff, infrastructure, and equipment can all be major limiting factors (8, 27, 28). Concomitantly, transportation of the critically ill patient between hospitals is not without risk. Given this context, it is unreasonable to expect that an institution can either set up or transport patients to an ECMO center during a pandemic in a reliable and safe way. Therefore, the consideration of $ECCO_2R$ in the appropriate patient can be resource-efficient and cost-effective. Given the concerns with disparities with COVID-19 outcomes, therapies that can be delivered where patients are may prove to be quite impactful (29–31).

The selection of $ECCO_2R$ for support of ARDS in place of VV ECMO is fundamentally based on whether oxygenation is adequate with mechanical ventilation to allow support with $ECCO_2R$. No prospective data exist to support this selection. A consensus of European experts was convened to address this and related issues using a modified Delphi method. With respect to $Pao_2/Fio_2$ ratio, an initiation target criterion was chosen as 100–200, with typical $Pao_2/Fio_2$ ratio being less than 150 (32). VV ECMO in contrast is typically initiated when the ratio is less than 100.

Patients who are on VV ECMO are occasionally not suitable for decannulation despite improvement in oxygenation due to dependence on sweep gas for $Co_2$ elimination. In these cases, de-escalating to $ECCO_2R$ can be been a valuable option. In addition, patients with COVID-19 may have elevated dead space ventilation even after completion of successful ECMO runs, and Hemolung may be a suitable small catheter alternative to continuing VV ECMO in these patients. This has allowed us to avoid using ECMO resources in the time of a surge when such resources were scarce.

## CONCLUSIONS AND LIMITATIONS

In this retrospective case series of 29 patients, we have demonstrated the efficacy of $ECCO_2R$ using the Hemolung RAS to improve respiratory acidosis in patients with severe hypercapnic respiratory failure due to COVID-19. This is the first reported use of $ECCO_2R$ in the United States for this patient population. Limitations of the current study are its small size and single-cohort retrospective nature. Even though it is a multiinstitutional study, a larger cohort of patients may provide additional outcome information. Although an EUA is not an FDA approval, a medical product authorized for emergency use under an EUA needs to have a pathway for physicians to make this technology available to patients across the country in different hospital settings. An intensivist would first need to seek approval from their hospital, followed by reaching out for training and device acquisition. Two hospitals who had not used the Hemolung device previously were able to use this technology during the pandemic.

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*Supported, in part, by the Ike Muslow, MD Endowed Chair for Healthcare Informatics, Louisiana State University Health Sciences Center, Shreveport, LA.*

*Dr. Conrad has received consulting fees from ALung Technologies, Inc. The remaining authors have disclosed that they do not have any conflicts of interest.*

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