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Extracorporeal Membrane Oxygenation and Coronavirus Disease 2019

To the Editor We read with great interest the Research Letter by Mustafa et al.1 The authors interpret their findings as demonstrating “promising outcomes” and as suggesting safety and effectiveness of venovenous extracorporeal membrane oxygenation (ECMO) in patients with coronavirus disease 2019 (COVID-19). However, several clarifications are required before valid conclusions are possible.

Eleven patients (28%) who were still in the intensive care unit (8 [20%] still receiving ECMO) were not included in the final data analysis. Thus, the validity of the outcome data is questionable. For example, the reported mortality of 15% is unusually low. In a recent report of 83 patients receiving ECMO for severe COVID-19–associated acute respiratory distress syndrome in a high-volume ECMO center experienced in the care of severe acute respiratory distress syndrome, 30 patients (36%) died at 60 days.2 Obviously, the 11 patients still in the intensive care unit at the time of data analysis need to be included in the final analysis, especially because survival was the primary end point. After all, if all of them should have subsequently died, the mortality would be 42.5%. In any case, a possible explanation for the considerable discrepancy in mortality between this and other reports would be welcomed.

The authors state that complications had been minimal. Besides the fact that minimal is not quantified, leaving the true incidence of complications unknown, the reported low incidence of complications in this population is remarkable. By contrast, of the 83 patients studied by Schmidt et al,4 4 patients (5%) and 11 patients (13%) developed hemorrhagic stroke and intravascular hemolysis, respectively, and 64 (77%) and 38 (46%) required transfusion of packed red blood cells and kidney replacement therapy, respectively. Because anticoagulation is an important treatment component of severe COVID-19,1,4 details regarding the anticoagulation management would be very helpful.

The authors report a mean time of 13 days from ECMO initiation to extubation. However, Figure 2 in their article1 suggests that 5 of 40 patients (12.5%) had not been extubated by the end of the observation period. This would imply that the reported mean time underestimates the ultimate intubation times. Thus, information regarding the final intubation times would be important.

In summary, while the reported outcomes seem promising, additional information is required before the findings can be placed in proper clinical perspective. Although the application of ECMO in COVID-19–associated acute respiratory distress syndrome has become an accepted option, the degree to which it should be used remains controversial.5

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To the Editor Mustafa et al1 reported impressive outcomes in 40 consecutive patients receiving extracorporeal membrane oxygenation (ECMO) for severe coronavirus disease 2019 (COVID-
19)-related acute respiratory distress syndrome.1 Recently, Schmidt et al2 described similarly encouraging results in 83 patients. However, they arrive at these outcomes through distinctly different approaches. Mustafa et al3 emphasize right ventricular support in addition to gas exchange. Acute right ventricular dysfunction is common in acute respiratory distress syndrome and is a negative prognostic indicator. The COVID-19 cohort may be at elevated risk of acute cor pulmonale because of coagulation disturbance and pulmonary thromboembolism.3 Mustafa et al3 applied a venopulmonary artery (V-PA) configuration through a single dual-lumen catheter inserted via the internal jugular vein. This strategy delivers oxygenated blood directly to the main pulmonary artery, draining the right atrium and bypassing the right ventricle. Schmidt et al2 applied venovenous ECMO by femoro-jugular cannulation returning oxygenated blood to the right atrium. However, 81% of patients were positioned prone during ECMO support. Prone positioning may provide right ventricular protection.4

Compared with traditional venovenous ECMO, V-PA ECMO results in negligible recirculation, and transpulmonary blood flow is rendered independent of right ventricle performance. V-PA ECMO ensures right ventricular support in the setting of increased pulmonary vascular resistance, eg, with patient-ventilator dysynchrony or pulmonary embolism (19% rate reported by Schmidt et al3). This V-PA approach may facilitate sedation, rehabilitation, and liberation from mechanical ventilation as illustrated by Mustafa et al,3 whereby 88% of patients were extubated by 13 days after ECMO initiation. Although ECMO duration was longer (mean [SD], 30 [3.6] days vs median [interquartile range], 20 [10-40] days) compared with Schmidt et al,2 rates of tracheostomy were 0% and 30%, respectively. Despite nuances in their respective approaches, protecting the right ventricle with early spontaneous ventilation or deploying prone positioning during ECMO may both have contributed to improved outcomes.

Although inferences from small cohort studies must be cautiously made, these studies offer independent, yet complementary visions of the future of extracorporeal respiratory support. ECMO goals must incorporate lung, right side of the heart, and diaphragm protection with strategies that mitigate deconditioning and permit expedient liberation from both ventilator and ECMO, limiting sequelae, such as ventilator-associated pneumonia and the need for tracheostomy. Preemptive mechanical support of the right side of the heart may have an important role to play. Clinical trials in ECMO are complex. However, a comparison of V-PA ECMO vs standard venovenous ECMO, with or without prone positioning, appears a compelling proposition based on these 2 recent studies.

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To the Editor We have read with great interest the report by Mustafa et al3 describing their venovenous extracorporeal membrane oxygenation (ECMO) experience in patients with severe coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome.1 Specifically, we commend their use of a dual-stage right atrium–to–pulmonary artery cannula, thereby promoting right ventricular (RV) support. Right ventricular dysfunction is a well-described complication of acute respiratory distress syndrome and is associated with increased mortality.2 Given the distinct pathophysiology involving the angiotensin-converting enzyme 2 receptor in combination with endothelial dysfunction, patients with COVID-19 acute respiratory distress syndrome may be at an increased risk of developing RV dysfunction.3 There have been multiple reports demonstrating RV failure in this particular patient population with abnormal RV longitudinal strain as an independent predictor of mortality.4 In our single-center experience, RV dysfunction in patients with COVID-19 supported with conventionally cannulated venovenous ECMO was common.

It is our belief that certain characteristics predispose patients with COVID-19 supported with ECMO to RV dysfunction. Of these factors, some may be iatrogenic in our zeal to avoid severe hypoxemia, while others are inherent to the disease process and patient characteristics.

Hyperactive delirium experienced by these patients is notoriously difficult to treat. The resultant use of sedatives may possess negative inotropic effects. Additionally, patient agitation also results in sympathetic surge, causing an increase in shunt fraction (ECMO flow:native flow), which in turn worsens hypoxemia and increases pulmonary vascular resistance.
A common remedy for this phenomenon is the use of β-blockade to decrease cardiac output, which may further depress an already strained RV. Furthermore, patients with COVID-19 typically require longer runs of extracorporeal ECMO therapy, often with higher flows, potentially resulting in chronically elevated right-sided preload. Finally, obesity has been reported as a significant comorbidity in this population by the Extra
corporeal Life Support Organization COVID-19 registry. In our experience, obesity was a major risk factor for RV dysfunction while receiving ECMO. It is likely that obesity acts synergistically with already altered respiratory mechanics by further
promoting atelectasis, barotrauma, and pulmonary hypertension. Moreover, obesity has been found to have a direct
effect on RV size, mass, and function in the general population.3

A myriad of factors may contribute to RV dysfunction in patients with COVID-19, and these effects can be exacerbated by interventions introduced during veno
enous ECMO. Using a dual-stage right atrium–to–pulmonary artery cannula takes the RV out of the equation, potentially contributing to the de
creased mortality reported by the authors.1 We await further
details of their experience with great excitement.

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To the Editor We read with interest the study by Mustafa et al1 describing the experience of venovenous extracorporeal mem
brane oxygenation (ECMO) for coronavirus disease 2019 (COVID-19)–induced acute respiratory distress syndrome (ARDS), published in JAMA Surgery.

This publication is one of the largest case series describing the experience of venovenous ECMO support for COVID-19–induced ARDS from the United States. Initial reports from China suggested a very high mortality (84%-100%) in pa
tients with COVID-19 who received ECMO support. However, recent studies from Europe have estimated the mortality bur
den in patients with COVID-19 supported with ECMO to be around 30%,2 which is similar to what is described in studies of patients with ARDS supported with ECMO outside the pan
demic. The study by Mustafa et al1 reported an impressive sur
vival benefit with ECMO support, with only 6 deaths of 40 pa
tients (15% mortality). We are curious to know the authors’ opinion on what may have contributed to this improvement when the entry criteria remain similar to those from experi
cenced ECMO centers in France.2

Driving pressure has been suggested to influence mortality in patients with ARDS, and steroid (dexamethasone) use has been reported to improve mortality in critically ill patients with COVID-19.3 Would the authors provide details about the reduc

tion in driving pressure after ECMO initiation and steroid administra
tion in their study cohort? The choice of cannulation configuration of dual-stage right atrium–to–pulmonary artery cannula use for ECMO support is intriguing. The authors state that this technique was chosen because of problems encountered in their first case with femoral-internal jugular cannulation config
uration. Would the authors provide details about the right ven
tricular function of the study patients before ECMO initiation? If most patients had right ventricular dysfunction, is it possible to hypothesize that the dual-lumen cannula technique from the right atrium to pulmonary artery, bypassing the right ventricle, led to favorable outcomes?

Despite use of large-bore dual-lumen cannulas and larger therapeutic anticoagulation targets, the authors did not report any bleeding or neurologic complications in their pa

tients, defying contemporary evidence.2,4 The blood flow in dual-lumen cannulas is generated by high pressures, and the large-bore dual-lumen cannulas are associated with in
creased intracranial and insertion site bleeding.5 We would ap
creciate the authors’ insight into the lack of bleeding and hem
orrhagic stroke complications in their study cohort.

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In Reply  We are writing in reference to the Letters to the Editors on our recently published article, “Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure.” We appreciate the comments from the authors. We would like to take this opportunity to not only respond to their queries, but also provide updates on the final outcomes of the patients presented in the article.

All 40 patients have now completed their hospital course. Thirty-three patients (82.5%) have been weaned off extracorporeal membrane oxygenation (ECMO). Twenty patients (50.0%) were discharged home, and 13 patients (32.5%) discharged to a short-term rehabilitation center are now home. The mean (SE) time from ECMO initiation to extubation was 11.1 (1.9) days. The mean (SE) time from extubation to ECMO decannulation was 22.2 (3.3) days. The total mean (SE) time receiving mechanical ventilation was 15.0 (2.2) days, time receiving ECMO was 33.3 (4.5) days, and hospitalization was 55.2 (5.7) days.

Five patients (12.5%) had significant bleeding requiring more than 5 units of blood transfusion within a 12-hour period. Four patients (10%) developed septic shock requiring 2 or more vasopressors. Three patients (7.5%) developed kidney failure requiring kidney replacement therapy while receiving ECMO. One patient (2.5%) required revision of the ECMO cannula, and 1 patient (2.5%) had a tracheostomy. One patient (2.5%) experienced a stroke. Overall, 7 patients (17.5%) did not survive, with 6 developing overwhelming sepsis.

The low mortality and morbidity in this cohort may be associated with our approach to ECMO support. Multiple studies have now indicated that patients with coronavirus disease 2019 (COVID-19) have a higher propensity of developing right ventricular failure, as Kopanyczyk et al highlight in their Letter. Although we did not measure right ventricular function in this group of patients, it is possible that our cannulation technique with the single-access, dual-stage right atrium–to–pulmonary artery cannula might have provided additional right-sided heart support. Other potential advantages of this cannula included single-site access to facilitate patient mobility and less mixing of deoxygenated blood. There were minimal cannula-associated complications or revisions. Extubating patients while receiving ECMO provided several benefits including weaning of sedatives, improving patient mobilization, and avoiding ventilator-associated trauma. Our ECMO teams, which included nurses, physician assistants, physical/respiratory therapists, and perfusionists among others, allowed for expert care to obtain our observed outcomes.

With regards to the details on ventilator and steroid management requested by Venkata et al, we feel that an in-depth description is beyond the scope of this Letter. We are currently putting together a thorough analysis and comparison of our ventilator management and sedation wean parameters, as well as our steroid and anticoagulation use protocols with those of other academic centers. We hope to summarize the findings in a separate article.

In conclusion, single-access, dual-stage venovenous ECMO with early extubation appears to be safe and effective in patients with COVID-19 respiratory failure. The low mortality and complication rates are likely the result of several aspects of our treatment protocol including cannulation technique, early extubation, and regular patient mobilization while receiving ECMO.

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CORRECTION

Error in Abstract and Results: The Review “Guidelines for Opioid Prescribing in Children and Adolescents After Surgery: An Expert Panel Opinion,” published online November 11, 2020, contained an error in the Abstract and Results. The statement “Twenty guideline statements were generated from a 2-day in-person meeting and subsequently reviewed, edited, and endorsed externally by pediatric surgical specialists, the American Pediatric Surgery Association Board of Governors, the American Academy of Pediatrics Section on Surgery Executive Committee, and the American College of Surgeons Board of Regents” should have omitted the American Academy of Pediatrics Section on Surgery Executive Committee. The error has been corrected online.