Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Essential Topics in the Management of Venovenous Extracorporeal Membrane Oxygenation in COVID-19 Acute Respiratory Distress Syndrome

FOR MORE THAN a year, patients around the world have dealt with the effects of coronavirus disease 2019 (COVID-19) infection, including acute respiratory distress syndrome (ARDS). Most patients with COVID-19 infection remain asymptomatic; however, approximately 5%-to-20% of patients develop severe ARDS requiring admission to the intensive care unit (ICU) and mechanical ventilation.[1-3] Strategies to manage this subset of patients include low-stretch mechanical ventilation, prone positioning, and neuromuscular blockade.[4] When these strategies fail due to refractory hypoxemia, severe hypercarbia, or requirement for severely injurious mechanical ventilation (MV) settings, venovenous extracorporeal membrane oxygenation (VV ECMO) can be an option. Venovenous ECMO allows lung rest ventilator settings, may permit safely waking the patient up to start physical therapy, and gives the patient time as a bridge to recovery or lung transplantation.[5] Management of mechanical circulatory support in COVID-19 ARDS requires a highly resourced multidisciplinary ICU team and the ability to nimbly develop protocols for care for this new patient population. Here the authors discuss some unique aspects of care using VV ECMO management in COVID-19 ARDS.

Lung Management: Ventilator-Induced Lung Injury, Patient Self-Induced Lung Injury (P-SILI) and Partial Paralysis

Early observation on the phenotypic expression of severe COVID-19 ARDS has demonstrated a spectrum between two variants: one with normal static lung compliance with refractory hypoxemia and the second with reduced lung compliance with hypoxemia.[6] In the high-compliance group, higher positive end-expiratory pressure (PEEP) levels may cause harm by compromising hemodynamics and cardiovascular performance without an improvement in oxygenation. In the low-compliance group, patients have stiff lungs that sometimes require injurious levels of MV to achieve oxygenation or carbon dioxide removal. These observations suggest that there is a spectrum of COVID-19 lung injury and MV management should be individualized. This is particularly salient when considering VV ECMO as a salvage therapy.

After instituting VV ECMO, clinicians can rest the lung by reducing PEEP and tidal volume size. Low-stretch ventilation is the standard of care for ARDS, as well including judicious PEEP and tidal volumes in the 4-to-6 mL/kg range.[7] The authors occasionally are asked to consider patients for prior VV ECMO to avoid intubation. Early VV ECMO in COVID-19 infection is possible, but there are no prognostic criteria or scoring systems that can predict the likely trajectory of a COVID-19 infection. Some patients will develop severe ARDS whereas others may recover with a short course of MV. At this time, only one published case report of preemptive ECMO cannulation prior to MV exists, and with the current intracranial hemorrhage (ICH) rate associated with VV ECMO in COVID patients, it would be hard to justify this as a standard practice.[8] Patients after cannulation should be kept sedated and paralyzed for the first seven-to-ten days with relatively high mean airway pressure while the minute ventilation is reduced. During this phase, any attempt at spontaneous breathing may be effective at promoting gas exchange, but often generates very large tidal volumes, and in the authors' practice appears to be accelerating lung injury. This is called P-SILI.[9] Subsequently, after an initial period of deep sedation and paralysis, the neuromuscular-blocking drugs can be weaned. This initial period of sedation/paralysis may be used for a trial of proning, which the authors now are performing on all patients with COVID ARDS receiving VV ECMO.[10,11]

After an initial period of complete paralysis, partial neuromuscular blockade targeting three-fourths or greater twitches can help bridge injured lung back to spontaneous ventilation. Low-dose neuromuscular-blocking drugs infusions can be used to decrease accessory muscle activation to limit tidal volumes while allowing the diaphragm to contract. This approach is controversial due to patients feeling awake while experiencing mild-to-moderate weakness. Multiple centers have used

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this strategy with success.[12,13] Low-dose paralysis patients usually require low-dose sedation and reassurance. Sedation can be achieved through a mixture of ketamine, lidocaine, propofol, as well as dexmedetomidine. Longer-acting medications, such as methadone, quetiapine, and diazepam, also can be used to create a steady state of sedation and anxiolysis while on VV ECMO. The goal of this strategy is to titrate tidal volumes below 4 and 6 mL/kg, even during spontaneous ventilation modes, so that the patient does not injure their lungs with high negative pressures. The patient still will be able to move and trigger inspiration cycles, but their breathing and potential coughing will not be as strong.

The second phase of lung management should include ventilating patients with spontaneous modes. This includes pressure-support ventilation or neurally-adjusted ventilation adjusted while maintaining low-stretch low tidal volumes.[14] This spontaneous patient-driven effort allows for the preservation of diaphragm function. Spontaneous ventilation may reduce ventilator desynchrony and, therefore, reduce sedation requirements. The team should have a strategy to deal with hypoxia. Maintenance of diaphragm function, as well as routine neurologic assessment with decreased sedation, are critical due to the high risk of intracranial hemorrhage (ICH) or if transplantation is considered.[15] Finally, the authors have found a high incidence of pneumothorax in late fibrotic COVID ARDS lungs. The extreme lung damage found in COVID ARDS can lead to pneumothorax as well as trapped lung. At the authors' institution, in 1,632 patients admitted to the ICU with COVID-19, 137 chest tubes were placed, and 92 (5.2%) were for pneumothorax. Chest tube placement can be done for patients on VV ECMO, however caution is advised because invasive procedures often are associated with bleeding.

ECMO management: CO_2 Retention and Extracorporeal CO_2 Removal

Initial management should be focused on using ECMO support to limit ventilator-induced lung injury and combat hypoxemia. Lung injury is proportional to the mechanical power applied to the lung, which takes into effect the tidal volume, driving pressure, respiratory rate, and inflation/deflation cycles, as well as the PEEP. The authors suggest weaning F_IO2 on the ventilator as well as PEEP support while keeping ECMO flows approximately two times greater than body surface area. Once patients have achieved steady state on the ventilator, ECMO weaning should commence.

Recently, the authors have encountered patients with persistent hypercarbia despite a minimal oxygen requirement. Several authors have suggested calculating CO_2 production based on metabolic and respiratory mechanics to predict successful weaning from sweep gas flow.[16,17] To ensure suitability for decannulation, extended sweep-off trials for some patients are necessary in the final stage of weaning VV ECMO. Many patients with COVID ARDS retain carbon dioxide, despite optimal ventilator settings. Minimal sweep on the ECMO circuit (0.5 L sweep) has not been able to assure that patients are ready for decannulation, and some patients have been recannulated despite tolerating minimal settings.

One concern for sweep-off trials is the concern for plasma leak, which was a problem in older oxygenators. The authors have performed multiple sweep-off trials with Quadrox oxygenators without circuit clotting or failure events. Personal communication with Gentinge, the Quadrox oxygenator manufacturer, assured us that they are not aware of any problems with this practice. In addition, the authors have reached out to other major centers that confirm safely using sweep-off trials. Importantly, with the sweep-off, no oxygen is being delivered to the circuit, so patients should be on minimal oxygen settings ($<$ or $= 0.3$ F_IO_2) prior to a sweep-off trial. Finally, bridge to hemolung, extracorporeal carbon dioxide removal, is feasible to allow for a smooth transition. The authors have used the hemolung in multiple patients to bridge off ECMO safely and allow the patient to continue spontaneously ventilating and participating in physical therapy.

Anticoagulation in VV ECMO: Bivalirudin, ICH, Tracheostomy

Several factors related to ECMO contribute to coagulopathy, including dilutional effects of the extracorporeal circuit, consumption of factors exposed to foreign surfaces, altered platelet surface protein function, hyperfibrinolysis, and acquired von Willebrand syndrome.[18,19] Recently, Rivosecchi et al. published their experience with using bivalirudin for all VV ECMO. They compared 162 patients with unfractionated heparin versus 133 patients with bivalirudin. They found a decrease in circuit thrombotic complications, fewer blood transfusion requirements, and a significant decrease in bleeding complications in the bivalirudin group.[20] Initially, in the cohort of COVID ECMO patients, the authors used unfractionated heparin as the anticoagulant of choice. Data demonstrate that COVID-19 patients are at increased risk for thrombotic and bleeding events.[21] Over the course of the past year, the authors have transitioned all of the COVID-19 ECMO patients to bivalirudin.

Acute respiratory distress syndrome due to COVID-19 not only occurs on the alveolar side but on the vascular side of the equation. Microthrombosis, microhemorrhaging, and macro bleeding, such as intracranial bleeding, all have been described in COVID-19.[22] Inflammatory markers, such as D-dimer, interleukin-6 and interleukin-1, lactate dehydrogenase, and ferritin, all have been demonstrated to be elevated in this patient population.[23] This particular facet of COVID-19 infection complicates the use of VV ECMO. These patients are at high risk for ICH due to numerous factors, including labile blood pressure, which is seen in most of these patients.[15,24]

Exposure to the ECMO tubing, oxygenator, and pump cause variable pharmacodynamics of opioid medications. The polyvinylchloride tubing and polymethylpentene oxygenator surfaces absorb lipophilic narcotic agents. Furthermore, after circuit exchanges or oxygenator exchanges, there might be wide fluctuation in sedation and awareness. Circuit changes events also may cause dynamic blood pressures changes.

These are critical moments in which the clinician should be closely involved. The authors try to control blood pressure and keep patients on a regimen of enteral labetalol and hydralazine. However, if patients are concurrently on vasopressor medications for sepsis or inotropic medications, such as epinephrine, to augment right ventricle function, there might be variable gastrointestinal absorption of these medications. With intravenous hydralazine on shortage, alternative antihypertensives, such as clonidine and propranolol, might be needed, as well as using sedatives as antihypertensives. Sedation with dexmedetomidine may help as well. The authors titrate antihypertensives to a goal systolic blood pressure below 160 mmHg if possible.

Cautiously consider early surgical tracheostomy to facilitate weaning paralytics and/or sedation. Clinicians need to balance the benefits against the elevated risk of bleeding with tracheostomy on ECMO.

Sedation, Analgesia, and Cough Suppression

Sedation management can be challenging in patients with COVID-19 on ECMO. Awake ECMO is a possibility with COVID ARDS; however, this needs to be balanced with the disease arc (early *v* late, compliant *v* fibrotic), as well as patient-specific factors. All patients with COVID-19 ARDS are placed on ECMO with the intention as a bridge to recovery; however, a subset of patients may need to bridge to transplantation. Therefore, awake VV ECMO allows for participation with physical therapy and decreases the risk for skin breakdown and muscle wasting. It is not uncommon to find extremely high doses of intravenous opioid infusions, benzodiazepine infusions, and propofol infusions; however, clear daily sedation weaning plans must be made to decrease the burden over days-to-weeks. Transition to longer-acting agents is ideal. Methylphenidate and quetiapine can be added to aid in neurocognition and wakefulness in extreme circumstances.

Persistent and refractory coughing is a common problem in the COVID ARDS population. Causes of coughing can be due to mechanical irritation as well as dysregulation of neuropulmonary stretch receptors. Severe pulmonary consolidation of the lungs also can cause air hunger and subjective sensation of suffocation. General strategies for cough suppression due to mechanical irritation include matching the appropriate tracheostomy tube to the airway. Essential aspects of tracheostomy design include variable cuff profiles such as foam cuffs, air cuffs, hi/lo cuffs, and cuffless designs. There also is variability in the horizontal and distal lengths as well as curvature. Finally, tracheostomy tubes can be constructed with wire reinforcement or PVC both flexible and rigid. Having a wide range of options to fit each particular patient's tracheostomy may help limit direct stimulation. For patients on VV ECMO, ventilator weaning while on ECMO is possible as long as they are able to tolerate the tracheostomy. Any plans for awake VV ECMO need to include appropriate strategies to mitigate coughing. Otherwise, ambulatory and awake VV ECMO will be difficult due to rapid changes in ECMO flows due to the coughing. Lidocaine infusions and nebulization can be used to address coughing, as well as guaifenesin and codeine. Low-dose ketamine infusions can help suppress coughing and by bronchodilation; however, ketamine may increase secretions. The team should have as-needed rescue medications ordered to treat refractory episodes of coughing. Finally, soft suctioning catheters, such as red rubber catheters, may be used to prevent exacerbation of airway injury during suctioning.

A secondary issue occurs with prone positioning on VV ECMO after tracheostomy. Proning with a tracheostomy presents a logistical challenge and safety concern including loss of airway protection, kinking of the tracheostomy tube, as well as direct pressure injury to the anterior neck. If patients on VV ECMO with tracheostomy require proning, then elective orotracheal intubation with temporary stoma closure may be considered.

Conclusion

Several challenges exist with the management of VV ECMO in COVID ARDS. Early institution of VV ECMO prior to MV is possible but has not become commonplace. After cannulation, the ventilator should be weaned and deep paralysis used to prevent lung injury and P-SILI. Partial paralysis can help transition off VV ECMO. Extracorporeal carbon dioxide removal is a tool that can be used to bridge patients with prolonged carbon dioxide retention after COVID ARDS. Bivalirudin is an alternative, potentially better, anticoagulation medication than unfractionated heparin. Sedation management should include long-acting agents as well as nontraditional medications such as lidocaine, ketamine, methadone, and dexmedetomidine. All these insights are not gospel, but rather emanate from a year-long effort to manage the sickest of the sick COVID ARDS patients.

Conflicts of Interest

None.

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