Extracorporeal CO_2 reduction for COVID-19: hypercapnic respiratory failure post extracorporeal membrane oxygenation

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SUMMARY

COVID-19-induced acute respiratory distress syndrome (ARDS) has challenged medical providers. In severe cases, patients present with poor lung compliance, requiring not only lung protective mechanical ventilation strategies, but also extracorporeal support. Due to the nature of the pandemic, the extracorporeal carbon dioxide removal device called Hemolung Respiratory Assist System became available under the Food and Drug Administration Emergency Use Authorization for patients with COVID-19-induced ARDS. This allowed application of the device to treat patients with recrudescent ARDS following an acute aspiration pneumonia following two previous veno-venous extracorporeal membrane oxidation treatment series, in the setting of hypercapnic respiratory acidosis.

BACKGROUND

The outbreak of SARS-CoV-2 caused the COVID-19 pandemic in March 2020. Severe cases of this illness are complicated by acute respiratory distress syndrome (ARDS). Clinical presentation of ARDS is often defined by the Berlin criteria: acute onset of Partial pressure of arterial oxygen (PaO_2) to Fraction of Inspired oxygen (FiO_2) ratio <300, chest radiograph opacities within three to four quadrants and without convincing heart failure aetiology.[1] Physiologically, ARDS is an inflammatory lung injury causing increased pulmonary vascular permeability, leading to alveolar oedema and ultimately loss of aerated lung parenchyma.[2] In severe cases, this can cause patients to present with poor lung compliance. COVID-19-related ARDS has shown to be similar when compared with the classic ARDS characterised by decreased lung compliance and increased lung weight, when normalised for ARDS severity.[2] ARDS management has many interventions, and among these lung protective ventilation is paramount to preventing ventilatory-induced lung injury (VILI). VILI includes atelectotrauma (subsequent atelectasis) and barotrauma (subsequent pneumothorax), which can exacerbate a patient's perfusion and ventilation deficits.[3] The goals of lung protective mechanical ventilation include tidal volume of 4–6 mL/kg (ideal body weight), plateau pressure <30 cmH_2O and driving pressure <15 cmH_2O.[4 5]

Clinical situations can present where therapies that are applied remain inadequate to provide appropriate oxygenation and ventilation. At this point we look to other options such as extracorporeal life support. Traditionally, this included venovenous extracorporeal oxygenation.

During this pandemic, the Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for ALung Technologies' Hemolung Respiratory Assist System (RAS). The Hemolung RAS functions as an extracorporeal carbon dioxide removal ($ECCO_2R$) device. Similar to VV-ECMO

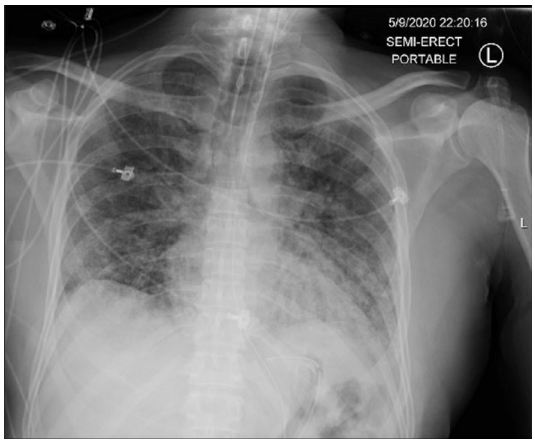

Figure 1 The patient's initial chest X-ray from admission showing bilateral infiltrates indicative of COVID-19 pneumonia.

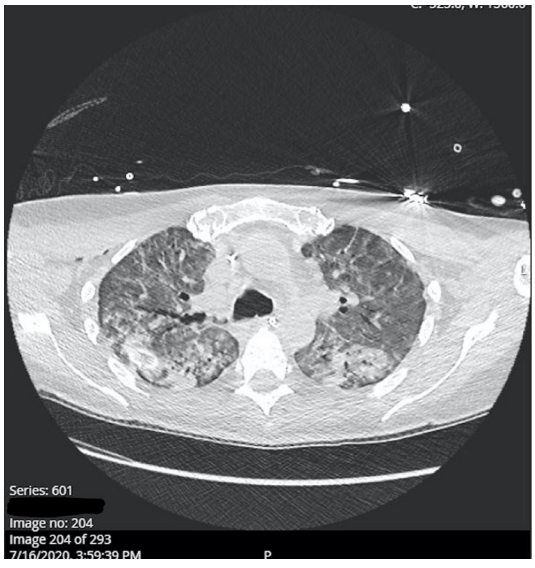

Figure 2 CT scan of the patient's chest showing recurrent acute respiratory distress syndrome and pneumonia, mid chest.

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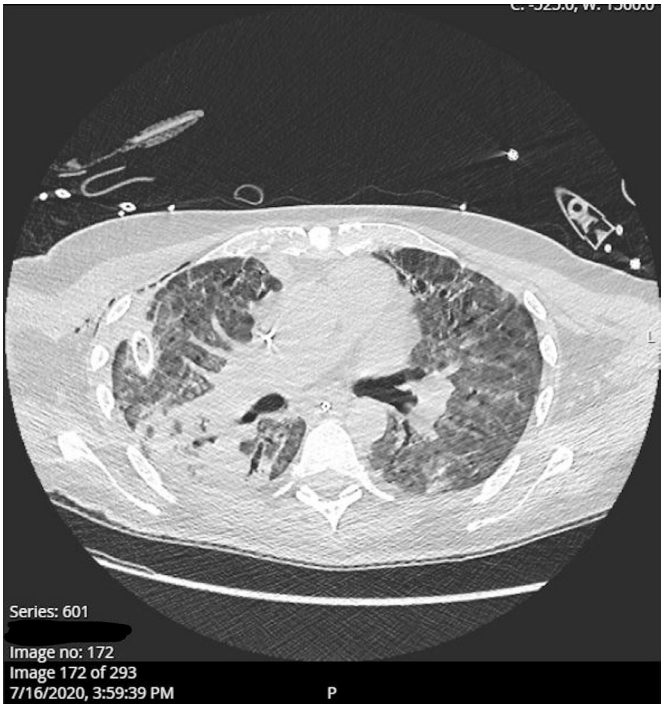

Figure 3 CT scan of the patient's chest showing recurrent acute respiratory distress syndrome and pneumonia, superior chest.

systems, $ECCO_2R$ systems provide partial lung support independent of lung mechanics. $ECCO_2R$ devices operate at much lower blood flow rates when compared with ECMO systems. Since carbon dioxide (CO_2) diffuses much more readily (due to higher solubility in plasma) when compared with oxygen (O_2), low-flow devices such as the Hemolung RAS provide CO_2 elimination,

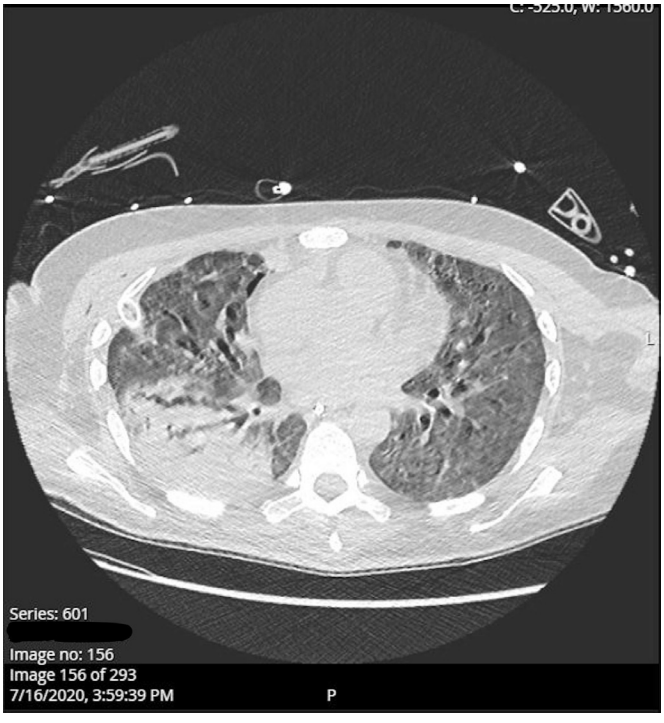

Figure 4 CT scan of the patient's chest showing recurrent acute respiratory distress syndrome and pneumonia, basilar view.

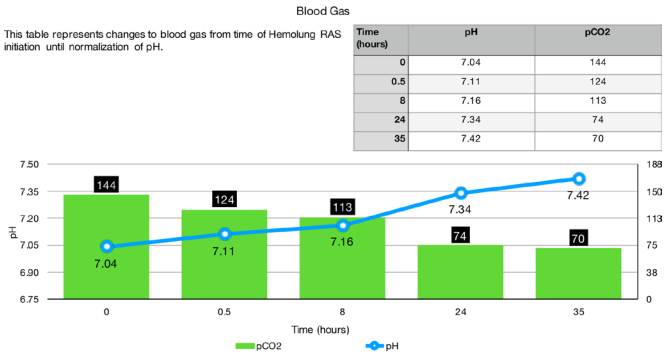

Figure 5 Changes to blood gas from time of Hemolung Respiratory Assist System (RAS) initiation until normalisation of pH. pCO_2, Partial pressure of carbon dioxide.

while ECMO systems can support both O_2 supplementation and CO_2 elimination.[6]

Hemolung RAS removes CO_2 by redirecting a portion of systemic circulation from the central vein through a dual lumen catheter via an integrated centrifugal pump towards a blood-gas exchanging membrane. A sweep gas (either room air or oxygen) is then pumped through the hollow fibres of the membrane, while the blood circulates around the fibres. The differing concentration of CO_2 between the blood and the sweep gas creates a CO_2 gradient, causing the CO_2 to diffuse from the blood, across the membrane, and into the sweep gas and terminally exhausted from the circuit through a gas outlet.[7] Extracorporeal carbon dioxide therapy is focused on management of patients with acute hypercapnic respiratory failure who fail non-invasive ventilation therapies, have difficulty weaning from invasive mechanical ventilation or require assistance with CO_2 removal to support lung protective mechanical ventilation.[8 9]

This report will describe the management of a patient with COVID-19-induced ARDS following multiple series of VV-ECMO treatments, with refractory respiratory acidosis subsequently managed with the Hemolung RAS device for $ECCO_2R$ under EUA by the FDA to facilitate rescue therapy.

CASE PRESENTATION

The patient is a 58-year-old man diagnosed with COVID-19 (14 April 2020) with no significant medical history, initially sent home to convalesce. He was admitted (19 April) to an outside hospital for acute hypoxaemic respiratory failure requiring supplemental O_2. His condition continued to deteriorate, requiring intensive care unit (ICU) admission (24 April) and invasive mechanical ventilation (29 April). He was treated with proning trial, hydroxychloroquine, azithromycin, convalescent plasma and broad-spectrum antibiotics for superimposed bacterial pneumonia. Despite these treatments, he suffered refractory hypercapnic and hypoxaemic respiratory failure, with associated elevated plateau pressures and low lung compliance.

He was transferred to our facility for VV-ECMO cannulation (9 May) in heart and vascular intensive care unit (HVICU) to be managed by the lung rescue team and ICU team. His chest X-ray revealed bilateral infiltrates consistent with COVID-19 ARDS (figure 1). After cannulation his condition began to improve. He underwent tracheostomy secondary to prolonged intubation (19 May) and his blood gas improved. While maintaining lung protective mechanical ventilation, we attempted to decannulate VV-ECMO (23 May) but were unsuccessful. He developed mixed respiratory failure and required VV-ECMO recannulation on the same day.

Table 1 Timeframe for the sweep wean from 10 down to 3, showing the relationship with pH, CO_2 and vent setting

Hemolung sweep wean						
	279 hours			284 hours	292 hours	316 hours
Wean placed on PC for TV approximately 4 mL/kg	Start sweep	281 hours	283 hours	Stop wean	8 hours on three sweep	31 hours on three sweep
Respiratory rate (breaths per minute)	38	38	38	38	38	28
Tidal volume (mL)	290	290	290	290	290	320
Plateau pressure	28	28	28	28	28	29
PEEP	5	5	5	5	5	5
pH	7.43	7.42	7.44	7.37	7.39	7.44
pCO_2	87	90	80	98	93	87
Sweep flow (L/min)	10	8	6	3	3	3
Blood flow (L/min)	0.43	0.46	0.44	0.44	0.46	0.44
Pump speed (RPM)	1400	1400	1400	1400	1400	1400

CO_2, carbon dioxide; PC, Pressure control; pCO_2, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; RPM, revolutions per minute; TV, tidal volume.

Our second attempt at decannulation was successful (11 June). While decannulated the patient was transferred to the medical intensive care unit (MICU) to optimise weaning from mechanical ventilation and further management. There he was liberated from the ventilator and transferred to the medical floor (7 July). He acutely decompensated following a suspected aspiration event (10 July). He again presented with acute hypercapnic respiratory failure refractory to urgent mechanical ventilation via tracheostomy. Hemolung RAS was initiated and the patient returned to HVICU under the care of the lung rescue team.

DIFFERENTIAL DIAGNOSIS

Considering the acuity of the patient's decline, it is reasonable to favour a new process. The differential spans a spectrum of pathology affecting ventilation, perfusion or both. Clinically, the patient presented with acute mixed respiratory failure. It is important to note the history of left lower lobe pulmonary embolism during this hospitalisation and that the patient was being treated with therapeutic Lovenox, making a recurrence less likely. On transfer to HVICU, he underwent chest X ray (CXR), which ruled out pneumothorax, and he was provided support for recrudescence of ARDS with bilateral diffuse opacities through his lung fields. Bedside nursing had reported suspected aspiration event on the floor earlier in the day. The patient did undergo barium swallow within the previous 48 hours, but failed with noted aspiration. In the ICU the patient underwent bronchoscopy with Bronchial alveolar lovage (BAL) and was started on empiric broad-spectrum antibiotics. The diagnosis was recrudescent ARDS exacerbated by acute superimposed acute bacterial pneumonia. This was confirmed later by chest CT (figures 2–4), along with resultant BAL notably growing *Stenotrophomonas* and *Pseudomonas*.

Table 2 pH and CO_2 after vent liberation with continued Hemolung wean down to a sweep of 0 and Hemolung liberation

Vent liberation					
	0 hour	3 hours	29 hours	59 hours	95 hours
	Vent liberation				Hemolung liberation
Pump flow (L/min)	0.42	0.41	0.42	0.41	Na
Pump speed (L/min)	1400	1400	1400	1400	Na
Sweep flow	3	2	1	0	Na
pH	7.39	7.42	7.36	7.42	7.45
pCO_2	56	53	58	50	51

CO_2, carbon dioxide; pCO_2, Partial pressure of carbon dioxide.

TREATMENT

Treatment included a course of methylprednisolone, along with broad-spectrum antibiotics that would later be tailored to sensitivity results from our BAL. We continued gentle diuresis to mitigate present as well as potentially accumulating pulmonary oedema. The patient was also maintained on inhaled prostaglandin for continued O_2 support via pulmonary vasodilation. Despite these treatments, along with a lung protective mechanical ventilatory strategy, the patient was unable to adequately clear CO_2. Initial mechanical ventilatory strategy was subsequently aggressive, tolerating elevated plateau pressures (>30 cmH_2O) temporarily

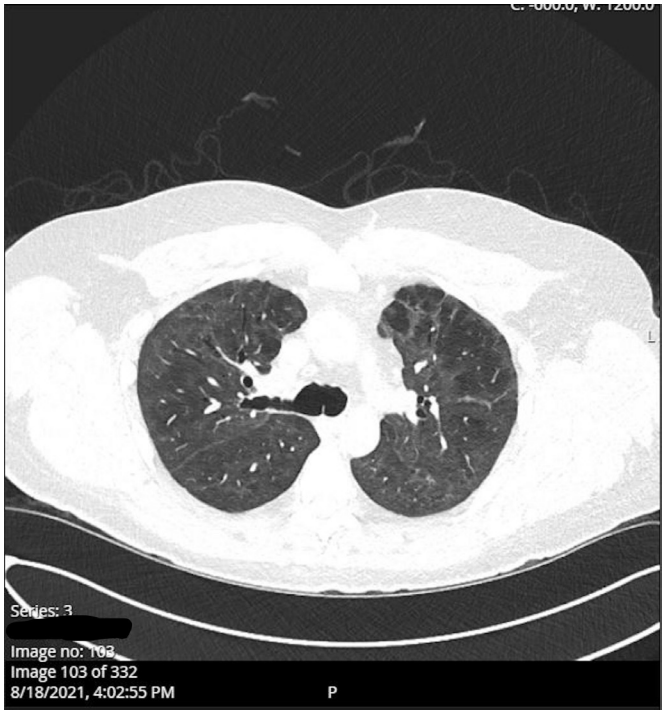

Figure 6 Most recent CT scan of the patient's chest showing resolved acute respiratory distress syndrome and pneumonia, superior chest.

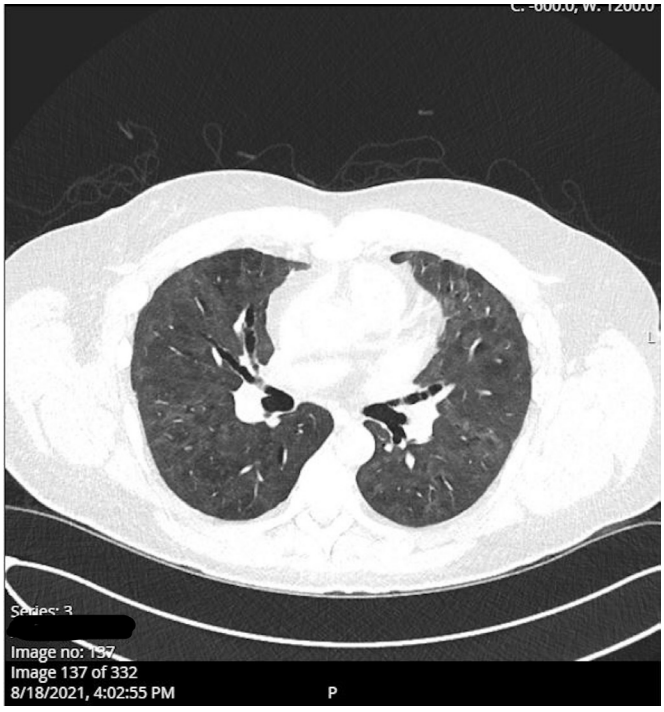

Figure 7 Most recent CT scan of the patient's chest showing resolved acute respiratory distress syndrome and pneumonia, mid-chest view.

to rescue the patient. Once his pH normalised, we re-evaluated our goals and decided to tolerate mild acidosis (goal of pH >7.25) and maintain plateau pressure <30 and tidal volume <6 cc/kg to mitigate further harm to the patient via VILI. Approximately 35 hours post cannulation of Hemolung RAS, we met our plateau pressure and tidal volume goals (figure 5). During the rescue effort the patient did sustain right apical pneumothorax requiring chest tube insertion.

Just over 1 week and 4 days into Hemolung RAS treatment, he was maintained on lung protective ventilation and we began to wean his sweep. His sweep was titrated in intervals over a 24-hour period, targeting a pH goal of >7.3. We did however restrict his sweep reduction to no less than 3 L/min to supplement CO_2 removal to prevent acidosis while facilitating spontaneous breathing trials (SBT) (table 1).

Once he was able to complete SBT we began periods off the ventilator until he was able to maintain unsupported continuously for 48 hours.

Now vent liberated, we again began to wean the Hemolung RAS sweep gas flow from 3 L/min to 0 L/min while still targeting pH of >7.3. He remained on a setting of 0 L/min of sweep for 36 hours and was decannulated from Hemolung RAS (table 2). He was then monitored in the ICU for the next 48 hours without extracorporeal support or mechanical ventilation before being transferred to medical floor to continue his recovery.

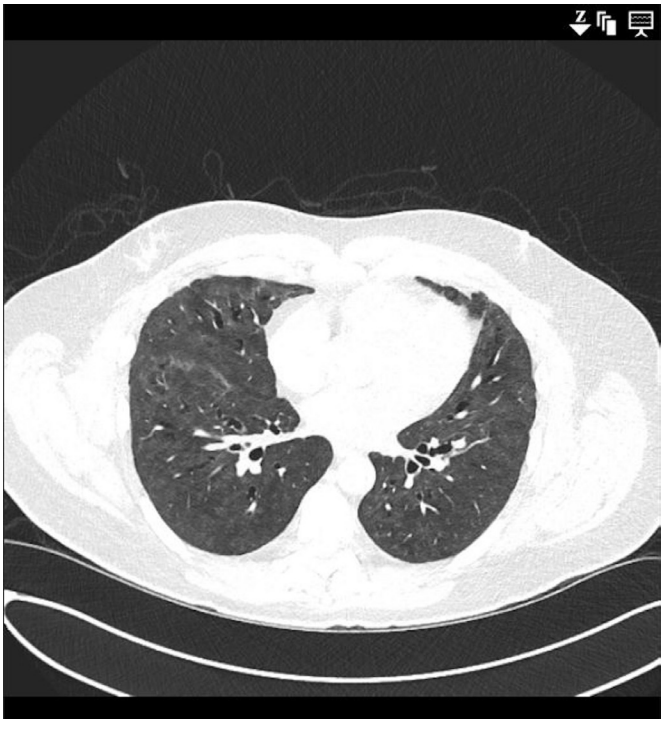

Figure 8 Most recent CT scan of the patient's chest showing resolved acute respiratory distress syndrome and pneumonia, basilar view.

OUTCOME AND FOLLOW-UP

After a 115-day length of stay that included 32 days (combined) on VV-ECMO and 38 days on $ECCO_2R$, the patient was discharged to an outpatient rehabilitation facility where he completed physical therapy for deconditioning and was released home. In a phone interview with the patient and his wife, the patient states he is doing well, his trach has been removed, and he is now on room air except for times of strenuous physical exertion. He is performing all his own activities of daily living (ADLs) and enjoys taking walks with his family. He underwent a CT scan in August of this year showing resolution of his COVID-19 pneumonia (figures 6–8).

DISCUSSION

In our case, the patient has presented with recrudescent ARDS secondary to aspiration pneumonitis. After evaluation the decision was made that attempting $ECCO_2R$ with Hemolung RAS was more favourable than a third course of ECMO. This decision was made with respect to the prolonged time this patient had already spent on ECMO, developing wounds at previous cannulation sites, and the reduced risk of cannulation complications using smaller catheter sets.[10]

The patient's primary issue was uncontrolled hypercarbia and subsequent respiratory acidosis while oxygenating. Hypercapnia can contribute to further complications of pulmonary hypertension, decreased myocardial contractility, increased intracranial pressure, reduced renal blood flow and release of endogenous catecholamine.[11] Attempting to treat hypercapnic acidosis in ARDS is complicated by lung protective ventilatory strategies which limit CO_2 removal. In a review of the SUPERNOVA trial, a large prospective multicentre international phase II study, it was concluded that $ECCO_2R$ was able to facilitate ultraprotective lung ventilation (4 cc/kg ideal body weight (IBW) and plateau pressure (pPlat) <25) in patients with moderate ARDS.[8] In this study the authors assessed multiple devices, one of which was Hemolung RAS.

Hemolung RAS would be set to a starting blood flow rate approximately 10% of the patient's cardiac output; as the flow rate increases, the rate of CO_2 removal would increase.[7] Initial sweep gas flow was set to 10 L/min.[7] In our case, once Hemolung RAS was initiated we were unable to use lung

Table 3 PH at 8 and 24 hours postcannulation to align with the SUPERNOVA trial data, tracked out to 35 hours demonstrating pH normalisation

Hemolung initiation					
	Precannulation	Postcannulation (30 min)	8 hours	24 hours	35 hours
Respiratory rate (breaths per minute)	34	34	40	32	32
Inspiratory pressure (cmH_2O)	22	22	28	34	26
Tidal volume (mL)	285–327	215–280	215–230	330–360	320–340
PEEP (cmH_2O)	7.5	7.5	7.5	5	5
pH	7.04	7.11	7.16	7.34	7.42
pCO_2	144	124	113	74	70
Sweep flow (L/min)	NA	10	10	10	10
Blood flow (L/min)	NA	0.45	0.45	0.48	0.47
Pump speed (RPM)		1400	1400	1400	1400

PEEP, Positive end expiratory pressure; RPM, rotations per minute.

protective ventilation to adequately correct hypercapnic respiratory acidosis. In a life-saving effort, higher pressures and larger tidal volumes were accepted initially. This aggressive strategy, in conjunction with Hemolung RAS, corrected his acidosis approximately 24 hours after treatment initialisation (table 3).

Over the next 11 hours, his compliance began to improve, allowing for lung protective goals. Approximately 1 week and 4 days after initiation of treatment, the patient's lung compliance improved, allowing transition from a pressure control to a volume control ventilatory mode. This provided a more stable minute ventilation measurement, allowing more accurate assessment of extrapulmonary gas exchange support required to maintain goal parameters (table 3).

While weaning the Hemolung RAS support, we used our experience with VV-ECMO management since data supporting weaning guidelines for $ECCO_2R$ in ARDS are limited. The Extracorporeal Life Support Organization (ELSO) does provide guidelines for weaning ECMO.[12] According to ELSO, when extracorporeal circulation is providing less than 30% of total support, native organ function may be adequate to indicate trial-off.[12] Trialling off consists of first adjusting the ventilator to acceptable settings as if the patient were without extracorporeal support and a trial period of sweep gas off.[13] Differences in weaning strategies in VV-ECMO are based on expert opinion rather than standardised evidence.[12]

Our weaning strategy consisted of maintaining lung protective ventilation, while titrating sweep gas and FiO_2 (in VV-ECMO) to a pH of >7.3 and PaO_2 >65. In general, our blood flow rates are maintained unless attempting to reduce haemolytic stress. As compliance improves, sedation requirements decrease and we can work towards pressure support mode of ventilation. If goals continue to be met, a 0 mL/min sweep trial will be performed. The 0 mL/min sweep trial provides a window of observation without extracorporeal support, while maintaining cannulation. This provides the ability to urgently reinitiate support.

When weaning Hemolung RAS, we basically maintained this strategy without the FiO_2 adjustment that the VV-ECMO would provide. In addition to this, we maintained the use of Hemolung RAS while the patient was liberated from mechanical ventilation. This strategy has the potential to facilitate shorter duration of positive pressure ventilation depending on the CO_2 removal requirements of the patient and the CO_2 removal capacity of Hemolung RAS. This has the potential to benefit our remaining clinical course significantly by reducing the risk of VILI and ventilator-associated pneumonia, which would further exacerbate lung tissue damage.[13] It is important to note that we must then assume a longer duration of extracorporeal support, which has its own risks of adverse events (ie, bloodstream infection, haemolysis, bleeding and thromboembolism).

Ultimately the Hemolung RAS assisted in CO_2 removal, facilitating our rescue of hypercapnic respiratory failure, maintenance of lung protective ventilation and hastening our mechanically ventilated time. The question remains, by how much?

Learning points

- Extracorporeal carbon dioxide removal ($ECCO_2R$) was used as an adjuvant treatment for acute hypercapnic respiratory failure.
- $ECCO_2R$ was used as an adjuvant treatment for acute respiratory distress syndrome with low lung compliance to facilitate lung protective mechanical ventilation.
- $ECCO_2R$ was used to hasten duration of mechanical ventilation.
- With a variety of extracorporeal support devices available, choosing appropriate therapy is dependent on the clinical scenario.
- Further research is needed to compare the carbon dioxide removal capacity of different extracorporeal support devices.

Correction notice This article has been corrected since published online. The corresponding author's email address has been changed from "John.taxiera@google.com" to "John.taxiera@gmail.com".

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