COVID-19 Respiratory Failure: Targeting Inflammation on VV-ECMO Support

Short Title: Successful VV-ECMO in Critical COVID-19

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Abstract

The outbreak of novel coronavirus (SARS-CoV-2) which causes the respiratory illness COVID-19 has led to unprecedented efforts at containment due to its rapid community spread, associated mortality, and lack of immunization and treatment. We herein detail a case of a young patient who suffered life-threatening disease and multi-organ failure. His clinical course involved rapid and profound respiratory decompensation such that he required support with veno-venous extracorporeal membrane oxygenation (VV-ECMO). He also demonstrated hyperinflammation (C-reactive protein peak 444.6 mg/L) with severe cytokine elevation (Interleukin-6 peak > 3,000 pg/mL). Through treatment targeting hyperinflammation he recovered from critical COVID-19 respiratory failure and required only 160 hours of VV-ECMO support. He is currently extubated without an oxygen requirement, showing signs of renal recovery on intermittent hemodialysis, and his repeat SARS-CoV-2 test is negative 21 days after his first positive test. We present the first successful case of VV-ECMO support to recovery of COVID-19 respiratory failure in North America.
Introduction

COVID-19 is a rapidly evolving pandemic with critically ill [1] patients and no proven treatments except supportive care. The 28-day mortality of critically ill COVID-19 patients is over 60% [1]. Older age, acute respiratory distress syndrome (ARDS) [1], hypertension, chronic kidney disease (Cheng et al. medRxiv 2020), and multi-system organ failure [1] are risk factors for mortality. Although most critical illness occurs in older patients, younger COVID-19 patients can be critically ill [1]. COVID-19 patients requiring critical care unit have higher levels of viral shedding suggesting an association with disease severity [2], but the dynamics between viral clearance and recovery from severe COVID-19 remain unclear. Further, cytokine storm and hyperinflammatory state with features overlapping CAR T-Cell therapy-related cytokine release syndrome (CRS), appears to be an emerging component of severe COVID-19 illness [2]. Clinicians have few therapeutic interventions undergoing investigation for COVID-19 to supplement a patient’s care. Our multi-disciplinary team of cardiology, cardiothoracic surgery, hematology/oncology, infectious disease, nephrology, and pulmonary/critical care medicine present the first successful report of VV-ECMO support for COVID-19 respiratory failure in North America while targeting hyperinflammation.

Case Report

On March 11th, an active 44-year-old male with known COVID-19 contacts and a family member with a viral prodrome presented with a 3-day history of shortness of breath and fever. Pertinent medical history included hypertension (on lisinopril) and hyperlipidemia (on atorvastatin). Pulse was 135 bpm, temperature 39.5 °C, blood pressure 159/91 mmHg, respiratory rate 20 breaths/minute, and oxygen saturation 95% on room air. The exam was otherwise unremarkable. Labs were notable for lymphopenia (450 cells/uL). Chest x-ray
revealed a small right upper lobe infiltrate. A viral panel and PCR for SARS-CoV-2 were negative. He was discharged on azithromycin and cefuroxime for community acquired pneumonia.

Twenty-four hours later he returned with persistent fever and worsening dyspnea. On exam, he remained tachycardic, febrile, and hypertensive with mildly increased work of breathing and diffuse rhonchi, but now oxygen saturation 96% on 3 L/min oxygen. Labs revealed worsening lymphopenia (370 cells/μL) and elevated C-reactive protein (41.5 mg/L). Repeat PCR for SARS-CoV-2 returned positive. He worsened rapidly requiring endo-tracheal intubation, lung-protective ventilation, inhaled epoprostenol, pronation within 12 hours, and escalation in fraction of inhaled oxygen (FiO2) to 80% and positive end-expiratory pressure (PEEP) to 14 cm H2O. At the time of pronation his partial pressure of arterial oxygen (PaO2):FiO2 ratio was 104. He did not require paralysis. Transthoracic echocardiogram was normal. He was continued on azithromycin and ceftriaxone and treated with hydroxychloroquine 400mg daily. He developed worsening PaO2:FiO2 (nadir 84), acute kidney injury, and abrupt onset hypotension that required dobutamine 5 mcg/kg/min and norepinephrine 15 mcg/min. He stabilized hemodynamically and LVEF on dobutamine 2.5mcg/kg/min was 50%. Creatine kinase increased from 312 U/L to 1,582 U/L. Troponin was negative. Interleukin (IL)-6 was severely elevated (2436.7 pg/mL, resulted hospital day 14). Based on the Extracorporeal Life Support Organization guidelines (www.elso.com) he met indication for VV-ECMO: hypoxemic respiratory failure with 80% mortality risk as predicted by PaO2:FiO2 <100 despite optimal care and was transferred on hospital day 4 (ECMO day 0). On arrival, vasoactive medications included dobutamine 2.5 mcg/kg/min, norepinephrine 6 mcg/min, and epoprostenol 50ng/kg/min, with pulse 105 bpm, arterial blood pressure 125/46 mmHg, oxygen saturation 90% on 100% FiO2 with tidal volume 6
mL/kg and PEEP 16 cmH₂O. Arterial blood gas showed pH 7.292, partial pressure of carbon
dioxide 45.7 mmHg, and PaO₂ 84 mmHg (PaO₂:FiO₂ 84).

We confirmed normal bi-ventricular function by echocardiogram, initiated femoral-femoral VV-
ECMO (4.8 L/min, 3700 RPM, 100% FiO₂, sweep 4 L/min), and started continuous renal
replacement therapy (CRRT). ECMO configuration: Quadrox-ID adult oxygenator and
Levitronix Centrimag device, 25F multi-stage cannula with tip the cavoatrial junction, 21F multi-
stage cannula in the abdominal inferior vena cava. We used a bifemoral approach to avoid
instrumentation near the airway and the need for transesophageal echocardiography used in
single cannula configuration.

His oxygen saturation increased to 97% and PaO₂ to 100 mmHg without changing ventilation
settings. Repeat IL-6 was severely elevated (>3,000 pg/mL, resulted hospital day 19). He was
continued on hydroxychloroquine 400 mg daily, azithromycin, and ceftriaxone.

By ECMO day 1 he was off epoprostenol, dobutamine, and norepinephrine; on 70% FiO₂ with
PaO₂ 72 mmHg; and on cisatracurium. Laboratory evaluation was notable for lymphopenia,
marked elevation in C-reactive protein, and hyperferritinemia (Table 1). We initiated
tocilizumab 800 mg every 8 hours for 3 doses, started hydralazine and clonidine for
hypertension, and removed net 2 L of fluid with CRRT.

On ECMO day 3, C-reactive protein decreased substantially, lymphopenia resolved (Figure 1
and Table 1), and antibiotic therapy completed. Lung function started to improve based on
reduced ventilator FiO₂ and ECMO sweep requirements (Figure 2).

On ECMO day 4 we started high-dose vitamin C 5,000 mg every 6 hours. His condition rapidly
improved and given an anticipated supply shortage, we discontinued hydroxychloroquine. By
ECMO day 7 he was on 21% FiO₂ on the ECMO circuit, sweep 0.5 L/min, PEEP 10 cmH₂O,
and tidal volume 6 mL/kg (Figure 2). We successfully decannulated him after 160 hours of VV-ECMO support and extubated him 4 days later. Repeat SARS-CoV-2 test was negative on hospital day 21 and oxygen saturation 99% on room air.

Discussion

We postulate that support with VV-ECMO, mechanical ventilation, and CRRT provided time for our patient to benefit from: 1) hydroxychloroquine possibly reduced viral load, 2) IL-6 receptor blockade likely abrogated hyperinflammation, and 3) high-dose vitamin C possibly reduced inflammation and enhanced lung recovery. Further, anecdotal data indicates that no COVID-19 patient with multi-organ failure has survived ECMO, prompting several institutions to set multi-organ failure as a contraindication. Based on our patient, multi-organ failure including acute renal failure may not signify an insurmountable scenario to contraindicate the use of VV-ECMO in COVID-19 patients.

Remdesivir is an investigational anti-viral agent in COVID-19, however, was contraindicated in our patient. A recent study reported reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens from patients treated with hydroxychloroquine [3]. Hydroxychloroquine may also suppress pro-inflammatory cytokines (Tumor Necrosis Factor (TNF)-alpha & IL-6) associated with coronavirus-induced ARDS [4]. Based on this information and limited anecdotal data, we treated our patient with hydroxychloroquine. In our patient, IL-6 levels continued to rise despite being on hydroxychloroquine and we cannot determine what effect hydroxychloroquine had if any on IL-6 levels.

Cytokine profiling from 40 COVID-19 patients from Wuhan, China demonstrated increased IL-1, monocyte chemotactic protein-1, TNF-alpha, IL-6, C-reactive protein, and ferritin levels (pre-print: Liu et al. MedRxiv 2020). C-reactive protein expression is induced by IL-6, is increased in
CRS, and may be clinically relevant as a marker of IL-6 activity [5]. Tocilizumab, an IL-6 receptor antagonist, is FDA approved and used in the management of CAR T-cell related CRS [5]. Based on partial clinical and biologic overlap with CRS, there is biologic plausibility to administer tocilizumab in severe and critical illness due to COVID-19. In support of this, 19 of 21 severely and critically ill COVID-19 patients in China treated with tocilizumab survived to discharge and >80% had improved fever, supplemental oxygenation needs, or inflammatory markers (pre-print: Xu et al. ChinaXiv 2020).

Chinese CDC oxygenation criteria for severe illness in COVID-19 parallel the ASTCT criteria for Grade 2 CRS, essentially requiring supplemental oxygen. Whereas the critical illness criteria in COVID-19 parallel the Grade 4 CRS criteria, essentially shock or requiring mechanical ventilation. In clinical trials, Grade 4 CRS is reversible in all patients treated with tocilizumab 8 mg/kg (maximum dose 800 mg) every 8 hours, maximum 3 doses in 24 hours [6]. Given the critical illness in our patient, we used this dosing regimen. After administration of tocilizumab, our patient has a rapid and sustained decrease in C-reactive protein (Figure 1). This demonstrates that tocilizumab given while on VV-ECMO is effective at blocking IL-6 signaling. The progressive improvement in oxygenation and decannulation from ECMO suggests blocking excessive IL-6 activity facilitates recovery from COVID-19 respiratory failure.

Vitamin C may also reduce the pro-inflammatory state and be beneficial in recovery of acute lung injury based on animal data [7]. While the CITRIS-ALI study [8] failed to demonstrate improvement in sepsis-related ARDS with vitamin C in primary endpoints, secondary analysis suggested lower mortality and more intensive care unit-free days with vitamin C (p < 0.05). Based on anecdotal reports on COVID-19 patients (reference not available), potential benefit, and lack of adverse effects [8], we elected to treat our patient with high-dose intravenous vitamin
C using the CITRIS-ALI protocol [8]. The rapid improvement in oxygenation and lung compliance in our patient after initiation of high dose vitamin C is impressive but could be coincidental.

Because of the rapid recovery of our patient it is enticing to speculate that targeting hyperinflammation in critical COVID-19 illness will reduce the duration of support needed from VV-ECMO and/or mechanical ventilation. However, the applicability of our single-patient experience must be cautioned. Neither tocilizumab nor vitamin C are FDA approved for use in COVID-19 patients and further investigation is needed to determine their benefit. Accordingly, our patient has been added to the Real world Evidence for Anti-Cytokine Therapy (REACT) in COVID-19 Registry.
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Figure Legends

Figure 1: Temporal relationship of tocilizumab and high-dose vitamin C therapy during venovenous ECMO (VV-ECMO) therapy with selected clinical laboratory results. The first dose of tocilizumab is denoted with a single dashed line and vitamin C with an alternating dashed line. A, C-reactive protein. B, Absolute lymphocyte count. C, Ferritin.

Figure 2: Temporal relationship of tocilizumab and high-dose vitamin C therapy during venovenous ECMO (VV-ECMO) therapy with oxygenation, mechanical ventilation, and ECMO parameters. The first dose of tocilizumab is denoted with a single dashed line and vitamin C with an alternating dashed line. A, Partial pressure of arterial oxygen to fraction of inhaled oxygen ratio (PaO2:FiO2). B, Fraction of inhaled oxygen (FiO2) on the ventilator and ECMO circuit. C, Positive end-expiratory pressure (PEEP, cm H₂O) and tidal volume indexed to ideal body weight (mL/kg). D, ECMO flow rate and sweep speed.
Table 1. Clinical Laboratory Results

|                                | Reference | ECMO Day 0 | ECMO Day 1 | ECMO Day 2 | ECMO Day 3 | ECMO Day 4 | ECMO Day 5 | ECMO Day 6 | ECMO Day 7 |
|--------------------------------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|
| White blood cell count (x10^3 per ul) | 3.4-10.8  | 12.8       | 11.4       | 9.6        | 9.9        | 13.2       | 16.3       | 15.7       | 13         |
| Red blood cell count (x10^6 per ul)   | 4.14-5.80 | 4.35       | 3.75       | 3.62       | 3.63       | 3.98       | 4.11       | 4.13       | 4.15       |
| Absolute neutrophil count (x10^3 per ul) | 1.4-7.0   | -          | 10.6       | 8.35       | 7.23       | 12.55      | 9.24       | 9.58       | 7.93       |
| Absolute lymphocyte count (x10^3 per ul) | 0.7-3.1   | -          | 0.23       | 0.38       | 0.89       | 1.45       | 0.98       | 2.36       | 1.56       |
| Platelet count (x10^9 per ul)            | 150-379   | 253        | 223        | 184        | 201        | 224        | 233        | 241        | 253        |
| Hemoglobin (g/dL)                        | 12.6-17.7 | 12.3       | 10.3       | 9.9        | 10         | 11.1       | 11.3       | 11.3       | 11.7       |
| Hematocrit (%)                           | 37.5-51   | 35.7       | 30.5       | 29.7       | 29.6       | 32.2       | 34.3       | 34.9       | 35.6       |
| Sodium (mmol/L)                          | 136-144   | 138        | 141        | 138        | 137        | 134        | 141        | 135        | 135        |
| Potassium (mmol/L)                       | 3.5-5.2   | 5.3        | 4.5        | 4.3        | 4.2        | 4          | 4.1        | 4.2        | 4.1        |
| Chloride (mmol/L)                        | 97-108    | 96         | 100        | 99         | 96         | 101        | 97         | 97         | 97         |
| Calcium (mg/dL)                          | 8.7-10.2  | 7.3        | 8.2        | 8.7        | 9.7        | 10         | 10.1       | 10.3       | 10         |
| Carbon dioxide (mmol/L)                  | 18-29     | 20         | 20         | 22         | 22         | 24         | 23         | 23         | 22         |
| Anion gap (mmol/L)                       | 5-19      | 22         | 21         | 17         | 16         | 14         | 17         | 15         | 16         |
| Glucose (mg/dL)                          | 65-99     | 103        | 99         | 108        | 100        | 95         | 110        | 112        | 114        |
| Blood urea nitrogen (mg/dL)              | 6-24      | 65         | 59         | 48         | 49         | 45         | 51         | 63         | 64         |
| Creatinine (mg/dL)                       | 0.76-1.27 | 6.35       | 5.77       | 4.22       | 3.18       | 2.86       | 3.08       | 3.27       | 3.29       |
|                                | 6.0-8.5 | 5.3 | 5.4 | 5.2 | 5.4 | 5.7 | 5.6 | 6.6 | 6.4 |
|--------------------------------|---------|-----|-----|-----|-----|-----|-----|-----|-----|
| Total Protein (g/dL)           |         |     |     |     |     |     |     |     |     |
| Albumin (g/dL)                 | 3.5-5.5 | 2.1 | 2.2 | 2.2 | 2.2 | 2.8 | 3.4 | 3.1 | 3.3 |
| Total bilirubin (mg/dL)        | 0.8-1.2 | 1.7 | 1.7 | 2   | 1.8 | 1.1 | 0.9 | 0.7 | 0.7 |
| Direct bilirubin (mg/dL)       | 0.0-0.4 | 1.7 | 1.5 | -   | 1.3 | 0.6 | 0.5 | 0.3 | 0.3 |
| Aspartate aminotransferase (U/L)| 0-40    | 132 | 108 | 109 | 150 | 284 | 195 | 150 | 99  |
| Alanine aminotransferase (U/L) | 0-44    | 69  | 59  | 63  | 81  | 190 | 208 | 189 | 159 |
| Alkaline phosphatase (U/L)     | 39-117  | 158 | 126 | 140 | 151 | 184 | 193 | 166 | 157 |
| Amylase (U/L)                  | 28-100  | -   | 73  | 69  | 65  | 94  | 122 | 195 | 283 |
| Lipase (U/L)                   | 0-59    | 42  | -   | -   | 32  | -   | -   | 135 | 244 |
| Arterial lactate (mmol/L)      | 0.36-1.25 | - | 1.78 | - | 1.12 | 1.68 | 1.33 | 1.29 | - |
| C-reactive protein (mg/L)      | 0.0-5.0 | - | 444.6 | 412.8 | 184.8 | 87.8 | 49.3 | 28.5 | 17 |
| Ferritin (ng/mL)               | 30-400  | - | 1,728 | 2,325 | 2,986 | 3,899 | 3,530 | 3,005 | 2,000 |
| Interleukin-6 (pg/mL)          | 0.0-15.5 | >3,000 | - | - | - | - | - | - |
| Creatine kinase (U/L)          | 24-204  | - | - | - | 651 | 377 | 193 | 644 | 394 |
| Creatine kinase-MB (ng/mL)     | 0.0-10.4 | - | - | - | 3.2 | 2.3 | 1.2 | 4 | 1 |
| Troponin I (ng/mL)             | 0.00-0.07 | - | - | - | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |
| Anti-thrombin III (%)          | 75-135  | - | 80 | - | - | - | - | - |
| D-Dimer (ug/mL)                | <= 0.49 | - | - | 13.24 | 17.77 | 11.73 | 8.66 | 10.46 | 15.45 |
| Fibrinogen (mg/dL)             | 175-475 | - | - | 741 | 608 | 537 | 470 | 416 | 364 |
Figure 1

A  
C-reactive protein

Concentration (mg/mL)

Time on VV-ECMO (days)

B  
Absolute lymphocyte count

Count (cells/µL)

Time on VV-ECMO (days)

C  
Ferritin

Concentration (ng/mL)

Time on VV-ECMO (days)
Figure 2

A

PaO2:FiO2 Ratio

Ratio

0 50 100 150 200 250 300

Time on VV-ECMO (days)

Vitamin C

Toilizumab

B

Ventilator and ECMO FiO2

FiO2 (percent)

0 20 40 60 80 100

Time on VV-ECMO (days)

Vitamin C

Toilizumab

C

Ventilation settings

Pressure (cmH2O)

0 5 10 15

Time on VV-ECMO (days)

Vitamin C

Toilizumab

PEEP

Tidal volume

D

ECMO settings

Rate (L/min)

0 2 4 6 8

Time on VV-ECMO (days)

Vitamin C

Toilizumab

Flow

Sweep
