Supplementary Online Content

Oppenheimer BW, Bakker J, Goldring RM, Teter K, Green DL, Berger KI. Increased Dead Space Ventilation and Refractory Hypercapnia in Patients with COVID-19: A Potential Marker of Thrombosis in the Pulmonary Vasculature

| Content                                      | Page |
|----------------------------------------------|------|
| eMethods                                     | 2    |
| eResults                                     | 3    |
| eFigure 1. Longitudinal clinical and physiologic data in patient #2 | 4    |
| eFigure 2. Longitudinal clinical and physiologic data in patient #3 | 5    |
| eFigure 3. Longitudinal clinical and physiologic data in patient #4 | 6    |
| eFigure 4. Clotted ECCOR membrane            | 7    |

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods

**Estimated dead space ventilation:**
Dead space ventilation was assessed since elevated values predispose to development of hypercapnia by reducing alveolar ventilation and CO₂ clearance. Dead space ventilation was estimated used the alveolar ventilation equation:

\[ P_a CO_2 = k \times \frac{\dot{V}CO_2}{V_e \left(1 - \frac{V_D}{V_T}\right)} \]

where:

- \( P_a CO_2 \) = arterial partial pressure for carbon dioxide (CO₂) expressed in mmHg
- \( k \) = constant (0.863) to convert units for metabolic rate expressed at standard temperature, pressure and dry conditions (STPD) to ventilation and gas exchange parameters that are expressed at body temperature, pressure and humidified conditions (BTPS);
- \( \dot{V}CO_2 \) = the metabolic rate of CO₂ production at STPD
- \( V_e \) = the exhaled minute ventilation expressed in liters per minute at BTPS
- \( V_D / V_T \) = the dead space fraction relative to the tidal volume

For this calculation the measured arterial blood gases of the patient were related to the corresponding values for exhaled minute ventilation. The metabolic rate for CO₂ production was assumed to be normal relative to body surface area (110 ml/min/m²). Dead space ventilation were not assessed while patients were treated with extracorporeal CO₂ removal (ECCOR) devices.

**Estimated right-to-left shunt:**
The fraction of blood flow comprising right-to-left shunt was estimated using the shunt equation:

\[ Shunt \ fraction = \frac{C_c' O_2 - C_a O_2}{C_c' O_2 - C_v O_2} \]

where:

- \( C_c' O_2 \) = the content of oxygen in ideal end-capillary blood
- \( C_a O_2 \) = the content of oxygen in arterial blood
- \( C_v O_2 \) = the content of oxygen in mixed venous blood

Blood oxygen contents were derived based on the measured arterial blood gases, the set fraction of inspired oxygen (FiO₂) and the measured hemoglobin concentration. Since patients were treated in strict respiratory isolation, invasive hemodynamic monitoring was not performed and there was no access to mixed venous blood. Thus, shunt calculations were performed using an estimated venous oxygen content, assuming normal cardiac output. While this assumption cannot be verified, patients were generally hemodynamically stable and the changes in estimated shunt fraction was accompanied by corresponding changes in either FiO₂ and/or P₅O₂.

**Extracorporeal CO₂ removal:**
All patients were treated with ECCOR using Novalung sLA membrane (Xenios, Heilbronn, Germany). ECCOR was performed without a mechanical pump by placing the afferent cannula in the femoral artery and the return cannula in the contralateral femoral vein. This approach relies on the patient’s native cardiac output to support blood flow through the extracorporeal circuit. For this reason, the blood flow was limited to 2 l/m. This approach utilizes relatively small-bore cannulas (arterial12-15F; venous 16-19F) that can be placed and eventually removed at the bedside foregoing transfer to and from the operating room. To minimize risk of bleeding at time of cannula removal, all arterial cannulas were placed using a suture mediated closure system (Perclose Proglide, Abbott, Lake Bluff, IL). To minimize the resistance on the return limb, the size of the venous cannula was at least 2F larger than the corresponding arterial cannula. Cannula sizes were individualized based on ultrasound measurements.
**eResults**

**$P_aCO_2$ and dead space ventilation**

All patients demonstrated a progressive increase of $V_D/V_T$ that began within the first 1-3 days after ICU admission. The simultaneous trend of $P_aCO_2$ was dictated by whether paralytic therapy was given. In 2 patients, paralytics were not administered and there was minimal change in $P_aCO_2$ reflecting respiratory control mediated increase in minute ventilation. In the other 2 patients, there was a simultaneous gradual increase in $P_aCO_2$ reflecting a fixed ventilation due to paralysis. In all patients, the $P_aCO_2$ remained below ~50 mmHg until values increased acutely to 62-100 mmHg despite maximal ventilatory support; this finding was attributable to a simultaneous increase in $V_D/V_T$ to 0.7 - 0.8. In this setting, ECCOR was initiated in all patients to control $P_aCO_2$ and acid-base status. In patient #3, ECCOR was discontinued on ICU day 9 and the patient was successfully extubated and discharged home.

**Blood coagulation**

There was a gradual increase in D-dimer that paralleled the increase in $V_D/V_T$ with peak values that occurred shortly after the peak $V_D/V_T$ in 3 patients; in the remaining patient, both parameters reached peak values simultaneously. The increase in D-dimer occurred while prothrombin time and activated partial thromboplastin time (aPTT) remained unchanged and within normal limits. Two patients demonstrated a simultaneous >50% reduction in platelet count; although prophylactic heparin was administered to all subjects, there was no evidence for heparin induced thrombocytopenia.

Shortly after the peak D-dimer level was noted, treatment with argatroban was initiated in 3 patients (which was followed by a gradual and progressive reduction in D-dimer levels. Unfractionated heparin was administered to the last patient; however, D-dimer levels remained elevated and unchanged with recurrent clotting of the ECCOR membrane. In this patient, the aPTT remained subtherapeutic despite progressive increase in heparin dose. On ICU day #10, the anticoagulation was changed to argatroban which was followed by immediate reduction in D-dimer and resolution of ECCOR membrane clotting.

**Cardiac findings and intrapulmonary shunt**

Initial cardiac echocardiography findings were similar in all patients with bilateral B-lines, dilated inferior vena cava (IVC>2cm) with minimal respiratory variation and dilated right ventricle (RV). All patients were treated with diuretics. By the 10th ICU day, 3 patients had a negative fluid balance (2-5 liters) while 1 remained with a neutral fluid balance. Nevertheless, intrapulmonary shunt fraction remained elevated in all patients during the initial few ICU days with values ranging from ~.03 to 0.4.

Repeat cardiac echocardiograms demonstrated evidence for RV strain in all patients when studies were performed after $V_D/V_T$ and D-dimer reached peak levels. Consequently, treatment with inotropic support (dobutamine: 2.5–8.0 ug/kg/min) was initiated in all patients; 2 individuals also received pulmonary vasodilator therapy using inhaled nitric oxide (iNO). Whereas right heart catheterization was not be performed to evaluate either cardiac output or pulmonary vascular resistance, there was a robust increase in systolic blood pressure and heart rate with initiation of inotropic therapy in all patients. Norepinephrine therapy was discontinued in the 2 patients that required vasopressor support.

Treatment with inotropes and pulmonary vasodilators was followed by reduction in intrapulmonary shunt in 3 patients. Concomitant increase in arterial oxygenation allowed weaning of F(IO2) and PEEP. In the remaining patient, intrapulmonary shunt remained unchanged and was accompanied by persistent elevation of D-dimer. Approximately 2 weeks into the ICU stay, iNO was weaned in the 3 patients that were treated with pulmonary vasodilators while sildenafil was started.
Supplementary eFigures

eFigure 1. Trends for PaCO₂, Vd/Vt, plasma D-dimer, and intrapulmonary shunt are shown for patient 1 over the course in the intensive care unit. Arrows indicate timing of interventions including institution of extracorporeal CO₂ removal (ECCOR), dobutamine, inhaled nitric oxide (iNO), and argatroban.
eFigure 2. Trends for $P_aCO_2$, $V_D/V_T$, plasma D-dimer, and intrapulmonary shunt are shown for patient 2 over the course in the intensive care unit. Arrows indicate timing of interventions including institution of extracorporeal CO$_2$ removal (ECCOR), dobutamine, inhaled nitric oxide (iNO), and argatroban.
eFigure 3. Trends for $P_aCO_2$, $V_d/V_T$, plasma D-dimer, and intrapulmonary shunt are shown for patient 3 over the course in the intensive care unit. Arrows indicate timing of interventions including institution of extracorporeal CO$_2$ removal (ECCOR), dobutamine, and argatroban.
eFigure 4. Clotted ECCOR membrane that occurred during anticoagulation with unfractionated heparin. Analysis of the white areas demonstrated fibrin formation and mixed inflammatory cell infiltrate with predominant neutrophil influx.