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Increased Dead Space Ventilation and Refractory Hypercapnia in Patients With Coronavirus Disease 2019: A Potential Marker of Thrombosis in the Pulmonary Vasculature

Beno W. Oppenheimer, MD[1,2]; Jan Bakker, MD[1]; Roberta M. Goldring, MD[1]; Katherine Teter, MD[3]; David L. Green, MD[2,4]; Kenneth I. Berger, MD[1]

Objectives: Mortality rates in intubated coronavirus disease 2019 patients remain markedly elevated. Some patients develop sudden refractory hypercapnia and hypoxemia not explained by worsening pulmonary parenchymal disease. This case series highlights clinical findings and management of coronavirus disease 2019 patients with refractory hypercapnia despite maximal/optimal ventilatory support. Hypercapnia could not be explained by worsening lung disease or other common factors, and thus, a pulmonary vascular etiology was suggested. The pillars of management were targeted to improve pulmonary vascular patency via aggressive anticoagulation and support right ventricular function.

Data Sources: Four consecutive patients with confirmed coronavirus disease 2019 infection with sudden hypercapnia and hypoxemia were included.

Data Synthesis: There was sequential development of: 1) severe hypercapnia attributable to marked elevation of dead space without radiographic changes; 2) concomitant coagulopathy manifest by an increase in D-dimer levels; 3) progressive shunt with consequent hypoxemia; and 4) right ventricular dysfunction. Management included extracorporeal Co_2 removal, direct thrombin inhibition, pulmonary vasodilators, and inotropic support. Marked improvement in Pao_2 allowed reduction in Fio_2 in all patients, extracorporeal Co_2 removal was discontinued in three patients over the ensuing 3 weeks, and one patient was discharged home.

Conclusions: We speculate that thromboinflammation with pulmonary microvasculature occlusion leads to a sudden increase in dead space and shunt resulting in severe hypercapnia and hypoxemia in coronavirus disease 2019 patients. Early identification of these physiologic and clinical biomarkers could trigger the institution of therapies aiming to reverse the hypercoagulable state and support right ventricular function.

Key Words: blood coagulation disorder; coronavirus disease 2019; hypercapnia; hypoxemia; respiratory dead space; respiratory failure

Since the commencement of the coronavirus disease 2019 (COVID-19) pandemic, ventilatory management has been a main focus of treatment. However, mortality rates in intubated patients remain markedly elevated (1). Many COVID-19 patients develop significant hypoxemia not readily explained by the extent of radiographic infiltrates, shedding doubt on the notion that patients fail mechanical ventilation solely due to progressive COVID-19 related pneumonia and/or acute respiratory distress syndrome (ARDS) (2); an additional role of pulmonary vascular dysfunction was suggested and the term COVID-19 ARDS was coined (3).

We describe treatment of four consecutive patients that exhibited an unexpected severe hypercapnia and hypoxemia unresponsive to traditional ventilatory adjustments. Hypercapnia and hypoxemia were not explainable by worsening lung disease since radiographs were stable; therefore, a progressive pulmonary microvascular occlusive process was suspected. Accordingly,

[1]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, NYU Grossman School of Medicine and André Cournand Pulmonary Physiology Laboratory, Bellevue Hospital, New York, NY.

[2]Department of Surgery, Manhattan VA, NY Harbor Healthcare System, New York, NY.

[3]Department of Surgery, New York University Langone Medical Center, New York, NY.

[4]Laura and Isaac Perlmutter Cancer Center, New York Langone Health, New York, NY.

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management was targeted to improve pulmonary vascular patency via aggressive anticoagulation, enhance pulmonary vascular perfusion, and support right ventricular (RV) function.

PATIENTS

Four consecutive COVID-19 patients (three male, one female; age: 52–66 yr) are described (**Table 1**). All patients presented with dyspnea, cough, fever, and bilateral pulmonary infiltrates (**Fig. 1**) and had at least one comorbidity including hypertension, diabetes mellitus, obesity, and asthma.

All patients received hydroxychloroquine and azithromycin. Based on sputum culture, one patient received additional treatment for Klebsiella and one received treatment for Candida. All patients received prophylactic low-molecular-weight heparin or unfractionated heparin. All were mechanically ventilated using a lung protective strategy and were initially proned, and two required muscle paralysis. Gas exchange data included estimated dead space to tidal volume ratio (VD/VT) and right-to-left shunt (**Electronic Supplement**, http://links.lww.com/CCX/A299).

CLINICAL COURSE

Figure 2 shows longitudinal data in a representative patient (remaining patients shown in **eFigures 1–3**, http://links.lww.com/CCX/A299). An acute increase in $PaCO_2$ was noted on day 5 of ICU admission, associated with a simultaneous increase in VD/VT (0.60–0.75). These findings occurred despite maximal ventilatory support such that extracorporeal Co_2 removal (ECCOR) was started (Electronic Supplement, http://links.lww.com/CCX/A299).
The acute increase in $PaCO_2$ was preceded by a gradual increase in VD/VT over the prior 2–3 days. Findings were similar in the other patients.

In all patients, D-dimer levels increased simultaneously with VD/VT where the peak values were measured approximately 1 day after the peak $PaCO_2$ and VD/VT. Prothrombin time and activated partial thromboplastin time remained within normal limits in all. In two patients, platelet count decreased by greater than 50% with negative serologic testing for heparin-induced thrombocytopenia. Treatment was changed to argatroban instead of heparin in three patients. This was associated with a reduction in D-dimer levels. One patient remained on an unfractionated heparin regimen initially but was subsequently changed to argatroban because of unchanged persistently elevated D-dimer levels and ecurrent clotting of the ECCOR filter (Electronic Supplement, http://links.lww.com/CCX/A299). Both problems resolved following this change to argatroban.

Initial echocardiography findings demonstrated bilateral B-lines, a dilated inferior vena cava (IVC) and dilated RV in all patients. Repeat echocardiograms at time of $PaCO_2$, VD/VT, and D-dimer peak levels demonstrated RV strain in all patients prompting inotrope therapy (dobutamine: 2.5–5.0 ug/kg.min). Two patients were started on inhaled nitric oxide (iNO) to decrease RV afterload and improve ventilation to perfusion ratio. There was robust increase in systolic blood pressure (range: 21–56 mm Hg). Intrapulmonary shunt decreased rapidly in three patients, allowing weaning of the FIO_2 and positive end-expiratory pressure (PEEP). In the remaining patient, shunt remained unchanged and was accompanied by persistently elevated D-dimer.

Approximately 2 weeks into the ICU stay, iNO was weaned in the two patients that were receiving this therapy and sildenafil was started. Approximately 3 weeks into the ICU course, ECCOR was withdrawn in three patients. Two patients are currently undergoing spontaneous breathing trials using pressure support ventilation. One patient was extubated and discharged home. Additional details regarding the clinical course are provided in the Electronic Supplement, http://links.lww.com/CCX/A299.

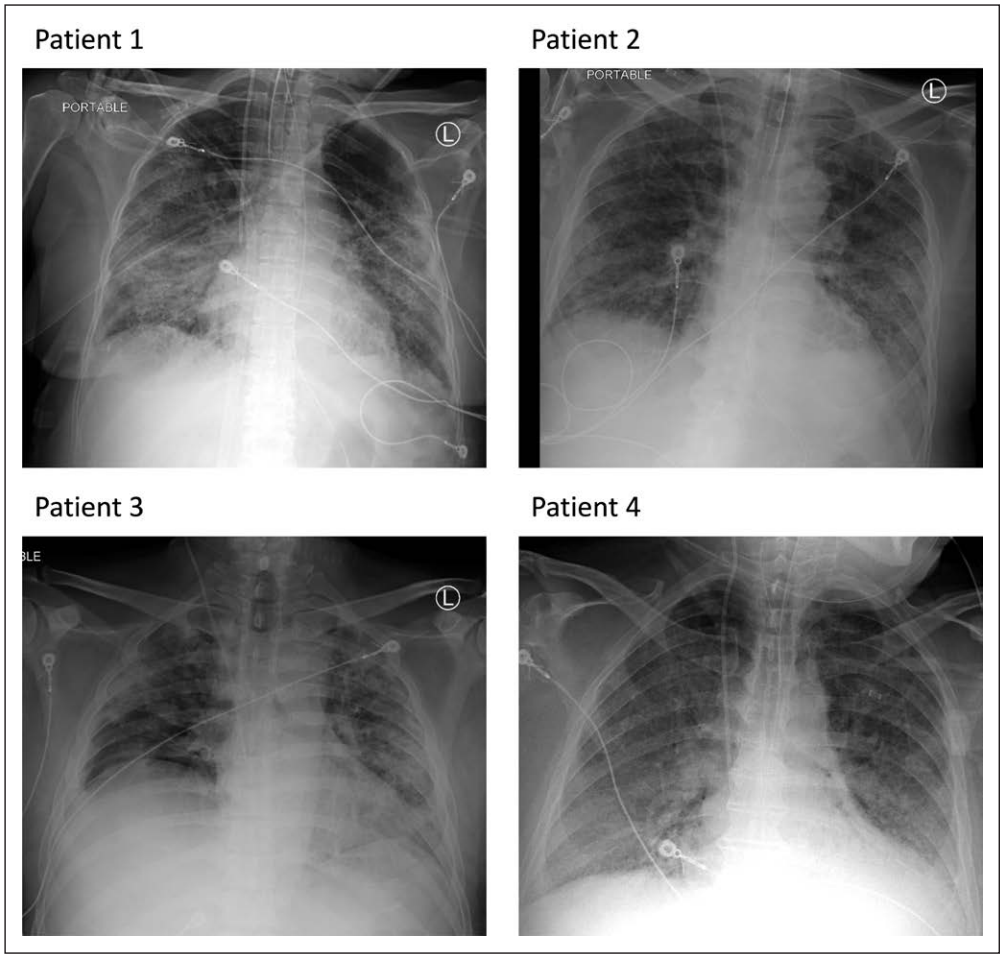

Figure 1. Chest radiographs from each patient at time of admission to the ICU. L = left side of the chest.

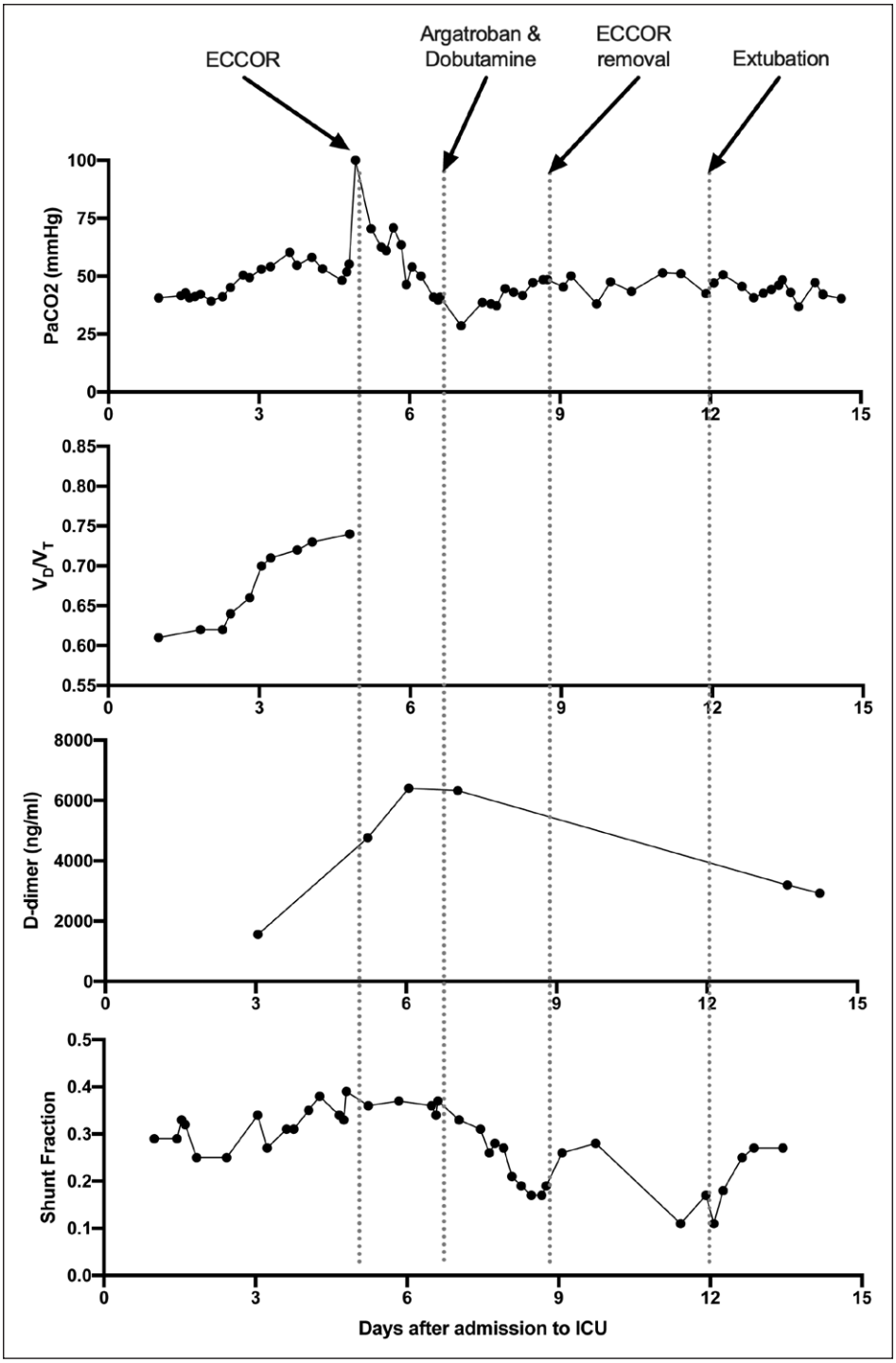

Figure 2. Trends for $Paco_2$, dead space to tidal volume ratio (V_D/V_T), plasma D-dimer, and intrapulmonary shunt are shown for a representative patient during care in the ICU. *Arrows* indicate timing of interventions including institution of extracorporeal Co_2 removal (ECCOR), dobutamine, and argatroban.

DISCUSSION

In four COVID-19 patients, we describe how unexplained refractory hypercapnia may be a clinical and physiologic manifestation of pulmonary microvascular occlusion due to thromboinflammation. An increase in dead space ventilation with stable chest radiographs in the presence of increasing D-dimer levels was the earliest marker of pulmonary microvascular disease (4) and could serve clinically as the "canary in the coal mine." While the acute increase in $Paco_2$ developed over several hours, the increase in dead space and D-dimer levels had been occurring over the preceding 2–3 days. Thus, early recognition of these findings could trigger immediate diagnostic studies and clinical interventions to optimize cardiopulmonary function. A clinical clue that reflects an elevated dead space is identification of an elevated minute ventilation in a patient with normal or increased $Paco_2$.

The evolution of hypercapnia, dead space, and D-dimer occurred over several days consistent with ongoing development of diffuse microvascular thrombi. Large vessel thromboembolic disease could have contributed; however, evaluation with contrast-enhanced chest CT was prohibitive. Regardless of location, the clinical manifestations and treatment of vascular occlusion would be similar.

Progressive intrapulmonary shunting also occurred in all patients. Hypoxemia initially responded to recruitment maneuvers and prone positioning, but subsequently became refractory. Given stable chest radiographs and presence of RV dysfunction, potential etiologies include low cardiac output, patent foramen ovale, or pulmonary infarcts. Shunt improved following administration of inotropes, iNO, and argatroban. Dobutamine was initiated to support RV function and improve hypoxemia by increasing mixed venous oxygen saturation. Although shunt could have also increased due to increased cardiac output, this effect may have been mitigated by limiting the maximal dobutamine dose to 5.0 μg/kg/min, by administering argatroban to counteract microvascular occlusion and by treatment with iNO in two patients to optimize ventilation to perfusion matching.

Baseline echocardiography demonstrated RV and IVC dilatation in the presence of B-lines on lung ultrasound. These findings are frequently attributed to volume overload prompting diuretic therapy. However, in the context of COVID-19, the abnormalities more likely reflect RV strain due to increased afterload caused by pulmonary vascular thrombosis, in addition to intrinsic lung disease with capillary leak (5, 6). In this circumstance, diuretic therapy may reduce preload and cardiac output with consequent worsening of mixed venous and arterial oxygen saturation. Furthermore, increasing PEEP to optimize oxygenation might further reduce preload and cardiac output with paradoxical worsening of arterial oxygen saturation, resulting in a vicious circle. These considerations support a recent

TABLE 1. Patient Characteristics Are Displayed Including Signs and Symptoms at Presentation, Underlying Medical Diseases, Severity of Illness, and Coronavirus Therapy

Demographic and Clinical Characteristic	Study Population ($n = 4$)
Age, range (yr)	52–66
Sex (male/female)	3/1
Symptoms on presentation (*n*)	
Dyspnea	4
Cough	4
Fever (*n*)	4
Chest radiograph (*n*)	
Ground glass opacities	4
Reticular marking	3
Underlying medical diseases (*n*)	
Hypertension	2
Diabetes mellitus	2
Obesity (body mass index > 30 kg/m^2)	3
Chronic obstructive pulmonary disease	2
Asthma	1
Maximal Sequential Organ Failure Assessment score (range)	6–13
Hospital day at time of intubation (range)	1–3
Coronavirus disease 2019 therapy (*n*)	
Hydroxychloroquine	4
Azithromycin	4
Dexamethasone	2

recommendation to use lower PEEP in COVID-19 when a vasogenic phenotype is present (3).

Recent reports have highlighted that COVID-19 pathogenesis includes primary injury to the vascular endothelium with activation of the clotting cascade and clinical evidence of in situ thrombosis and ischemic arterial events (5). A recent autopsy study demonstrated perivascular lymphocytic inflammation with pulmonary vascular thrombi in small vessels and alveolar capillaries (6). Concomitant dilation of the right heart suggests increased RV afterload and myocardial strain. Thus, although COVID-19 presents with hypoxemic respiratory failure and pulmonary infiltrates, the nature of the pulmonary disease differs from traditional ARDS. Cardiorespiratory supportive care requires consideration of the vasocentric features to optimize clinical outcome (3).

COVID coagulopathy is characterized by hyperfibrinogenemia, which correlates with elevated IL-6 levels, elevated factor VIII activity, high D-dimer, mild hypoprothrombinemia, and mild to moderate thrombocytopenia (7). Overt disseminated intravascular coagulation is not characteristic but may convey increased mortality. Elevated D-dimers correlate with disease severity and prognosis and anticoagulation lowers markers of hypercoagulation and may improve outcome (8–10). Coagulation studies demonstrated changes in viscoelastic properties associated with increased clot strength. There is evidence for mildly decreased antithrombin levels (Ranucci et al [7]) and presence of antiphospholipid antibody and lupus anticoagulant (11).

The optimal anticoagulant management of COVID-19 is unknown. Breakthrough clotting events occur with heparin therapy, as observed in our patients. Argatroban was administered based on its ability to inhibit clot bound thrombin in addition to free thrombin (12). Additionally, argatroban is not cofactor-dependent, as antithrombin may be decreased by hepatic dysfunction and consumption following thrombin generation. Other reports have suggested consideration of tissue plasminogen activator for a similar indication (13, 14). While argatroban was effective in our patients, its role as the anticoagulant of choice requires further study.

Refractory hypercapnia and severe respiratory acidosis prompted treatment with ECCOR. In these patients, we used a pumpless ECCOR system that uses arteriovenous pressure gradients to drive blood flow across the gas exchange membrane (15). Hemodynamic status was relatively preserved in all patients and each individuals' intrinsic cardiac function was sufficient to support this therapeutic strategy. The advantages of this modality include the feasibility of obtaining vascular access and performing decannulation at the bedside, foregoing transfer to the operating room. The placement of a Perclose device (Abbot, Lake Bluff, IL) prior to insertion of the arterial cannula allows for the easy decannulation with minimal bleeding. The main disadvantage of this system is that while Co_2 removal is readily achievable, blood flow through the extracorporeal membrane is inadequate to increase blood oxygenation.

In conclusion, development of hypercapnia, increased dead space, intrapulmonary shunt, and RV strain may be attributable to pulmonary microvascular occlusion due to an hypercoagulable state, as manifested by simultaneously increased D-dimer levels. Although the precise location of vascular occlusion cannot be definitely determined, the progression of disease over several days is more consistent with evolution of diffuse microvascular thrombi rather than large vessel thromboembolic disease. Early identification of these biomarkers could trigger therapies targeted to optimize anticoagulation, maintain pulmonary vascular patency, and support RV function while instituting lung protective ventilation. The utility of other inflammatory biomarkers could not be assessed in this retrospective case series. Physiologically directed therapies were successful in correcting blood gases in all patients; three were weaned from ECCOR and one was discharged home.

This work was performed at Manhattan VA, NY Harbor Healthcare System.

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For information regarding this article, E-mail: beno.oppenheimer@nyumc.org

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