

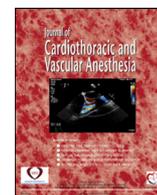


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents lists available at [ScienceDirect](#)

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: [www.jcvaonline.com](http://www.jcvaonline.com)

## Case Report

# Role of Tissue Plasminogen Activator for Diffuse Pulmonary Microemboli in Coronavirus Disease 2019 Patient

Samit Ghia, MD<sup>1</sup>, Himani Bhatt, DO, MPA<sup>2</sup>, Michael Lazar, MD

*Mount Sinai Morningside and West Hospitals, Icahn School of Medicine, New York, NY*

### ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related hypercoagulability has been of great interest in the pathophysiology of coronavirus disease 2019 (COVID-19). Many patients have clinical findings of dead-space ventilation, similar to pulmonary embolism. Herein, a patient who presented with COVID-19 pneumonia and whose condition rapidly deteriorated to respiratory failure requiring intubation is described. Tissue plasminogen activator (tPA) was administered because of concern of pulmonary microemboli, with improvement of respiratory status and extubation within 24 hours. Patients with COVID-19 infection have an increased risk of thrombus formation,<sup>1</sup> and the administration of tPA may benefit these patients by immediately lysing diffuse thrombi and improving gas exchange.

© 2020 Elsevier Inc. All rights reserved.

*Key Words:* Hypercoagulability; coronavirus disease 2019; thrombolysis; respiratory failure; pulmonary embolism

SINCE ITS origination in Wuhan, China, coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly, leading to a worldwide pandemic. There has been a growing interest in the role of hypercoagulability that has been demonstrated in COVID-19 patients, with many often presenting with diffuse thrombosis.<sup>2</sup> Some of the thrombotic disease has manifested as widespread microemboli, with a large clot burden leading to the morbidity and mortality seen with this disease.

Appropriate anticoagulation therapy has become the subject of much discussion, and multiple hospitals have put forth institutional policies to address the initiation of anticoagulation in moderate-to-severe disease. However, it is unclear how many patients rapidly develop diffuse thrombus formation and what the optimal timing of therapy is. Thrombolytic therapy (ie, tissue plasminogen activator [tPA]) may have a role in treating

these patients and may prevent further deterioration secondary to large clot burden.

This case report adhered to the applicable EQUATOR guideline. The appropriate Health Insurance Portability and Accountability Act authorization was obtained from the patient's healthcare proxy for the submission of this report.

### Case Report

An 81-year-old male, with a history of hypertension, hyperlipidemia, gastric ulcer, aortic valve replacement, and chronic lymphocytic leukemia, presented to the emergency room complaining of fever and cough for 10 days and new-onset shortness of breath with chest pain for 24 hours. He had a mild lymphocytosis; elevated inflammatory markers (ie, ferritin, C-reactive protein, lactate dehydrogenase, D-dimer, and procalcitonin); and bilateral opacities on chest radiograph. The patient was admitted with viral pneumonia as a result of moderate/severe COVID-19.<sup>1</sup> He was started on hydroxychloroquine, azithromycin, and broad-spectrum antibiotics. While in the emergency room, his oxygenation worsened on non-

<sup>1</sup>Address reprint requests to Samit Ghia, MD, 1111 Amsterdam Ave, New York, NY 10025.

E-mail address: [samit.ghia@mounsinai.org](mailto:samit.ghia@mounsinai.org) (S. Ghia).

<sup>2</sup>H. Bhatt is a clinical consultant for NeoChord LLC, St Louis Park, MN.

rebreather, and he was transitioned to bilevel positive airway pressure (bi-PAP) and screened into the intensive care unit (ICU).

On admission to the ICU, methylprednisolone, aspirin, and subcutaneous heparin were added to his medication regimen. Because of frequent episodes of supraventricular tachycardia and atrial fibrillation, he was started on apixaban, 5 mg daily, per cardiology recommendation. His QTc increased to 538, therefore the hydroxychloroquine was discontinued. In addition, the patient began self-proning daily for 8-hour shifts, with no appreciable improvement.

On admission day 6, the patient received a dose of tocilizumab for an elevated interleukin-6 level, and therapeutic enoxaparin was started in place of apixaban because of concern for insufficient anticoagulation. However, his condition continued to decompensate, with persistent hypoxia (partial pressure of arterial oxygen [PaO<sub>2</sub>] of 43 mmHg on 100% fraction of inspired oxygen [FiO<sub>2</sub>] on bi-PAP), and he experienced worsening respiratory distress and was intubated on day 7. After intubation, his oxygenation initially improved on ventilator settings, with tidal volumes of 400 mL, respiratory rates of 22, positive end-expiratory pressure of 12, and FiO<sub>2</sub> of 100%. However, dead-space ventilation was apparent, with persistent hypercarbia and alveolar pressures of 12-to-15 mmHg. Because of recent respiratory deterioration and suspicion for diffuse pulmonary microthrombi, tPA was administered without further workup or diagnostic studies. The dose administered was a 6 mg bolus and 2 mg per hour infusion over 22 hours.

During the thrombolytic infusion, the P/F (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio improved to 142 (PaO<sub>2</sub> of 114 mmHg on an FiO<sub>2</sub> of 80%) on day 8. After completion of the tPA infusion, the patient was started on a heparin infusion. By day 9, his ventilator was weaned to an FiO<sub>2</sub> of 40%, he tolerated a spontaneous breathing trial, and he was extubated to bi-PAP at 40%. Arterial blood gas showed resolution of the dead-space ventilation (partial pressure of arterial carbon dioxide of 30.5 mmHg), and his P/F ratio drastically increased to 610 (PaO<sub>2</sub> of 244 mmHg on an FiO<sub>2</sub> of 40%). Table 1 summarizes pulmonary and arterial gas measurements around the time of tPA administration. D-dimers, elevated at 2.8 upon presentation, increased to 16.91 after initiation of tPA before trending downward. However, the lytic and anticoagulation treatment were complicated by melena consistent with an upper gastrointestinal bleed. After discontinuation of heparin and aspirin, 2 U of packed red blood cells were given to treat an acute blood loss

anemia. He transitioned to non-rebreather over the next few days, was transferred out of the ICU on day 13, and was discharged on day 28.

## Discussion

In COVID-19, caused by SARS-CoV-2, injury to the alveoli is believed to be the major cause of hypoxia and acute respiratory distress syndrome (ARDS).<sup>3</sup> Hypercoagulation also appears to be involved in the disease process, not merely sepsis-related disseminated intravascular coagulation. Coagulation markers, including D-dimer and fibrinogen, have been elevated in patients with COVID-19. Implementation of anticoagulation has decreased morbidity and mortality,<sup>2</sup> and autopsies have found diffuse alveolar damage and microvascular thrombi in the lungs.<sup>4</sup>

The exact mechanism of hypercoagulability is not yet understood. One postulation points to the functional receptor of the virus. Angiotensin-converting enzyme (ACE) II is a counter-regulatory component of the renin-angiotensin system. Angiotensin II, which is cleaved by ACE II, is proinflammatory, prothrombotic, and vasoconstrictive. ACE II protects against excessive angiotensin II and some animal models have shown that COVID-19 is associated with a downregulation of the enzyme.<sup>5</sup>

Pulmonary embolism and diffuse pulmonary microemboli cause dead-space ventilation by impairing appropriate alveolar perfusion. The findings seen in the present patient were hypoxia, persistent hypercarbia in high-minute ventilation, and normal lung compliance. Although the patient was receiving systemic anticoagulation, it possibly had limited efficacy because of the high clot burden theorized in patients with moderate/severe COVID-19. In these patients, even though there are no prospective studies evaluating the efficacy of tPA in COVID-19 because of its novelty, the authors hypothesize that thrombolytic therapy dissolves current microemboli while subsequent anticoagulation prevents re clotting and improves gas exchange, lung perfusion, and oxygenation.

Lung compliance in ARDS worsens as the severity increases. As the lung injury worsens, leading to more edema, lung weight, and atelectasis, the volume of air in the lungs is displaced, leading to dyspnea and hypoxia. However, many patients with severe COVID-19 pneumonia have severe hypoxia, with normal lung compliance and poor responsiveness to increasing levels of positive end-expiratory pressure. These patients, much like the patient in the present case, have a

Table 1  
Pulmonary/Gas Measurements

	PaCO <sub>2</sub> (mmHg)	PaO <sub>2</sub> (mmHg)	MV (L/min)	PEEP (cm H <sub>2</sub> O)	FiO <sub>2</sub> (%)	P/F
Pre-tPA	46	43	10.5	14	100	43
During tPA	52	114	15.6	14	80	142.5
Post-tPA	30.5	244	11.2	8	40	610

Abbreviations: FiO<sub>2</sub>, fraction of inspired oxygen; MV, minute ventilation; PaO<sub>2</sub>, partial pressure of arterial oxygen; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; P/F, PaO<sub>2</sub>/FiO<sub>2</sub>; tPA, tissue plasminogen activator.

pulmonary physiology more like dead-space ventilation than shunting, suggestive of pulmonary embolism or pulmonary microemboli. As these patients remain on the ventilator longer, some progress to a more traditional ARDS.

In the present case, there was significant clinical improvement possibly because the disease had not progressed to advanced stages. The patient described herein was the only patient in the unit who was intubated for less than 72 hours. With the development of alveolar injury and pulmonary fibrosis, impaired gas exchange may be irreversible. Wang et al. discussed 3 patients in whom tPA transiently improved P/F ratios but had little effect on the patients' clinical condition. Important to note, all 3 patients were intubated and on vasopressor support, alluding to late stages of COVID-19.<sup>6</sup> The authors of the present case report credit the improvement in their patient to tPA because his condition continued to deteriorate while he received other anticoagulants. The authors postulated that anticoagulants, such as heparin or apixaban, were ineffective because they block clot formation but do not induce clot breakdown.<sup>7</sup> However, it must be acknowledged that the patient was receiving concomitant anticoagulants that may have affected his hospital course.

When considering tPA, risks and benefits must be appreciated. The benefits have been noted in approved indications such as PE, ischemic stroke, and ST-elevation myocardial infarction. Nonetheless, sometimes the risk outweighs the benefit in contraindicated states, such as signs and symptoms of active bleeding.<sup>8</sup> Bleeding or hemorrhage is a serious risk of thrombolytic therapy, as was seen in the present patient, and coagulation studies can guide its titration.<sup>9</sup> Additional

investigation will help shed light on the legitimacy of thrombolytic therapy and its ideal timing, dosing, and criteria for inclusion.

Samit Ghia: no financial disclosures, no conflicts of interest.

Himani Bhatt: financial disclosure - Clinical consultant for Neochord, LLC, no conflicts of interest.

Michael Lazar: no financial disclosures, no conflicts of interest.

## References

- 1 Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol* 2020;215:108427.
- 2 Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* 2020;18:1559–61.
- 3 Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J* 2020;55:2000607.
- 4 Zhang T, Sun LX, Feng RE. [Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019]. *Zhonghua Jie He Hu Xi Za Zhi* 2020;43:E040.
- 5 Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol* 2020;92:726–30.
- 6 Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *J Thromb Haemost* 2020;18:752–5.
- 7 Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: A review. *West J Emerg Med* 2015;16:11–7.
- 8 Hughes RE, Tadi P, Bollu PC. TPA therapy. Treasure Island, FL. StatPearls Publishing 2020.
- 9 Moore HB, Barrett CD, Moore EE, et al. Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)? *J Trauma Acute Care Surg* 2020;88:713–4.