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Case Report

# Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case report

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**Abstract:**

*Coagulopathy has proven to be a common complication of the novel coronavirus SARS-CoV-2[1]. Some of the COVID-19 associated pneumonia patients exhibit relatively preserved lung compliance and high alveolar-arterial oxygen gradient. Pathology reports consistently demonstrate diffuse pulmonary microthrombi on autopsy, consistent with a vascular occlusive etiology of respiratory failure rather than the more classic findings of ARDS[2]. Pulmonary microthrombi induced respiratory failure is very difficult to prove because the patients are so critically ill that transfer to CT suit to do CTPA often becomes unsafe for the patients. Moreover, performing V/Q scan is increasingly difficult in such settings. Here we report a case of severe COVID-19 associated respiratory failure who was treated with tissue plasminogen activator (tPA) on clinical ground.*

## Introduction

A hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19, meeting International Society on Thrombosis and Haemostasis criteria for disseminated intravascular coagulation (DIC), whereas only 0.6% of patients who survive meet these criteria[2]. Additionally, it has become clear that this is not a bleeding diathesis but rather a predominantly prothrombotic DIC with high venous thromboembolism rates, elevated D-dimer level, high fibrinogen levels in concert with low antithrombin level, and pulmonary congestion with microvascular thrombosis and occlusion on pathology in addition to mounting experience with high rate of central line thrombosis and vascular occlusive event (eg, ischemic limbs, strokes) observed by those who care for critically ill COVID-19 patients [3-8]. There is evidence in both animals and humans that fibrinolytic therapy in acute lung injury and acute respiratory distress syndrome (ARDS) improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS. This would be expected to be seen in patients with ARDS and concomitant diagnoses of DIC on their laboratory values such as what is observed in more than 70% of those who die of COVID-19[9-11].

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## Case report:

A 45-year-old obese (BMI>30 kg/$m^2$) female with a history of Systemic Hypertension, Diabetes Mellitus & Hypothyroidism presented to an outside hospital with fever & cough for 6 days, loose motion for 4 days, increasing respiratory distress for 3 days. COVID 19 test (RT-PCR) was positive. Following admission her oxygen requirement increased dramatically from 2 L $O_2$ /min supplementation via nasal prong to 15 L $O_2$ /min in non-rebreathing mask (NRB) over 1 day. Then she was shifted to our ICU for proper management. On admission, she was tachypneic [RR 32 breath/min], tachycardia [HR 132/min], temperature 102° F, oxygen saturation ($SpO_2$) 69% with 15 L $O_2$ /min with NRB mask. Her blood gas analysis showed severe hypoxemia with partial pressure of oxygen/FiO2 (P/F) ratio of 41. She was immediate intubated & put on mechanical ventilator. The ECG showed sinus tachycardia, bedside transthoracic echocardiogram showed a preserved EF with no regional wall motion abnormalities (RMWA). Her D-Dimer level was high along with Ferritin, CRP & LDH (lactate dehydrogenase) better if you mention the values. Her ventilator strategies have been optimized and other supporting managements have been introduced including steroid ( high dose methylprednisolone). Decision was taken to administer Tocilizumab (humanized anti-human interleukin 6 receptor monoclonal antibody), 6 mg/kg divided into 2 dose, given in 12 hours apart. She showed good response to those therapy and her $FiO_2$ could be reduced to 40% with improvement of P/F ratio 237 with improvement of overall lung compliance. But on 4$^{th}$ day of ICU admission new onset hypoxemia developed with P/F ratio of 96, lung also became very stiff with lung compliance decreased sharply. Her $FiO_2$ requirement remains >90% despite maximal ventilator strategies. Prone positioning was adopted but there were little improvements on hypoxemia (P/F ratio ranged between 90 to 120). We were unable to do CTPA due to severe hypoxemia and high risk during transfer of patient to CT suite.

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On 5th Day of ICU admission a decision was made to administer tPA (Alteplase). 25 mg tPA was administered intravenously over 2 hours, followed by 25 mg tPA infused over next 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complications. At 16 hours of tPA infusion her P/F ratio improved to 217. LMWH (Enoxaparin) was given in therapeutic dose throughout the ICU stay. As her P/F ratio improved she was placed back to supine position. Her oxygen requirement decreased gradually & weaning trial could be commenced successfully. She was liberated from ventilator and transitioned to High Flow Nasal Cannula (HFNC) in 7th day of ICU admission. On 10th day, her oxygen requirement decreased from HFNC to 2 L $O_2$/min trough nasal prong. Then she was transferred to Medicine ward for next management.

**Discussion:**

The clinical course of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) meets the criteria for Acute Respiratory Distress Syndrome (ARDS) in many patients, the unfavorable course of which ultimately leads rapidly to death. In cases with fatal outcome, the pathophysiology of ARDS has been related to a hyperimmune reaction that increases the progressive worsening of lung function [12]. During the hyperimmune inflammatory reaction, activation of complement leads to the formation of C3a and C5a that elicit recruitment of lymphocytes, macrophages, monocytes, and neutrophils, responsible in turn for the massive local release of proinflammatory cytokines IL-1, IL-6, IL-8 and interferon-γ[13]. In addition, leukocytes mobilized at the injury site exert a potent proinflammatory effect, causing extensive vascular-endothelial damage, alveolar epithelial cell damage, and microvascular thrombosis[14]. The functional implications of the specific pathogenesis of ARDS contribute to a progressive worsening of the ventilation/perfusion imbalance and to the loss of reactive hypoxic vasoconstriction, with striking component of intrapulmonary microvascular thrombosis. Specifically, massive alveolar endothelial damage leading to a progressive pulmonary syndrome with microvascular thrombosis has been proposed as the primary mechanism of respiratory distress associated with COVID-19, suggesting the acronym MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as the pathophysiological hypothesis of the atypical ARDS produced by COVID-19 infection [15].

Anticoagulation with low molecular weight heparin appears to be associated with lower mortality in the subset of patients who meet the criteria for sepsis-induced coagulopathy or have a remarkably high D-dimer as reported in observational studies. However, the relationship of heparin use at prophylactic doses with mortality rates is still supported by limited evidence and high-risk of confounding factors[16]. Beyond observational studies, randomized controlled trials are necessary to assign a causal association between heparin use and clinical outcomes in severe COVID-19 patients. However, in refractory respiratory failure in which disseminated intrapulmonary microvascular thrombosis may be the most significant mechanism in SARS-CoV-2 induced progressive respiratory distress, anticoagulant therapy may play a limited role in this terminal phase of the dying patient. Fibrinolytic agents could be a better alternative to promote the necessary clot lysis at this preagonal clinical stage, not to prevent the growth and extension of the thrombus mediated by anticoagulants. The scientific rationale for fibrinolytic therapy to improve lung function in seriously ill patients with COVID-19 is supported by several considerations, the main one is there are currently few ARDS therapies proven to be effective other than respiratory therapy [17]. Fibrinolytic therapy on various animal models has been shown to be effective in acute lung injury in different preclinical studies[18]. A small phase 1 human clinical trial in patients with terminal ARDS (unrelated to SARS-CoV-2) showed that either urokinase or streptokinase led to a significant improvement in arterial blood oxygenation and significant lower mortality rates than expected[19]. Tissue-type plasminogen activator (tPA) has higher clot lysis efficacy than urokinase and streptokinase without increased bleeding risk. Severe/life-threatening bleeding was 0.4–0.8% in myocardial infarction and submassive pulmonary embolism patients treated with 50 or 100 mg of tPA over 90 to 120 min followed immediately by a therapeutic heparin drip[20,21]. Clearly, the risk of adverse events from tPA is far outweighed by the certainty of death in COVID-19 patients meeting eligibility criteria for this treatment[22].

In summary, the pathophysiology of SARS-CoV-2 could be explained in part by vascular endothelial dysfunction and pulmonary microthrombosis, potentially responsive to fibrinolytic treatment with tPA. This therapeutic option, under the indication of compassionate off-label use, should be carefully considered in the management of critically ill COVID-19 patients with severe refractory respiratory failure requiring intensive support. This salvage therapeutic option could be decisive in patients with severe COVID-19 infection and refractory ARDS with no available treatment alternative.

**Conflict of Interest:**

The authors declare that there are no conflicts of interest regarding the publication of this article.

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