Case Series

# Role of low-dose tissue plasminogen activator in patients with refractory hypoxia due to presumed microthrombi in pulmonary vasculature in coronavirus disease 2019: A case series and review of the literature

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## ABSTRACT

Severe hypoxia due to coronavirus disease 2019 (COVID-19) is challenging in the intensive care unit (ICU). It is often unresponsive to mechanical ventilation at high positive end-expiratory pressure and the fraction of inspired oxygen combination. The cause of such worsening hypoxia may be microvascular thrombosis in the pulmonary vascular system because of the procoagulant nature of COVID-19 infection. Confirming the diagnosis with computed tomographic pulmonary angiography is not always possible, as the patients are too sick to be shifted. Tissue plasminogen activator (tPA) is recommended for pulmonary thromboembolism with hypotension and worsening hypoxia, as confirmed by computed tomography pulmonary angiography. However, its role in worsening hypoxia because of presumed microthrombi in the pulmonary vasculature in COVID-19 is unclear. We present six cases from our ICU where we used low-dose tPA in COVID-19 refractory hypoxia with presumed microthrombi in the pulmonary vasculature (oligemic lung field, refractory hypoxia, increased D dimer, electrocardiographic features of pulmonary embolism, and right ventricular strain on echocardiography). Oxygenation improved within 6 h and was maintained for up to 48 h in all patients. Therefore, there is a possible role of microthrombi in the mechanism of hypoxia in this setting. An early decision to start low-dose tPA may improve the outcome. However, all patients finally succumbed to sepsis and multiorgan failure later in their course. A systematic review of the literature has also been performed on the mechanism of thrombosis and the use of tPA in hypoxia due to COVID-19.

**KEY WORDS:** Coronavirus disease 2019, pulmonary thromboembolism, refractory hypoxia, tissue plasminogen activator, tissue plasminogen activator

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## INTRODUCTION

Severe hypoxia in coronavirus disease 2019 (COVID-19) is a challenge in patients admitted to the intensive care

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unit (ICU). Most times, this hypoxia is unresponsive to usual treatments such as noninvasive ventilation and mechanical ventilation with a high positive end-expiratory pressure and the fraction of inspired oxygen (FiO2) combination.[1,2] COVID-19 has been predominantly linked with thrombotic events, which makes it different from other causes of hypoxia. Viral RNA extensively damages the endothelium, causes activation of factor XI, activation of platelets, and the release of von Willebrand factor, thrombin, and fibrin generation.[3] Autopsy studies have also demonstrated pulmonary arterial thrombosis in COVID-19-related acute respiratory distress syndrome (ARDS).[4] There is an increased incidence of the thromboembolic phenomenon in COVID-19 patients even after anticoagulation with low molecular weight heparin (LMWH). In addition, there is also increased bleeding risk due to disseminated intravascular coagulation and thrombocytopenia. COVID-19 ARDS has been classified into low elastance (L-type) and high elastance (H-type). Since the L-type phenotype is characterized by oligemic lung fields and normal compliance, the mechanism of hypoxia in such cases could be due to poor perfusion because of widespread microthrombi in the pulmonary circulation. Therefore, theoretically, it may respond to thrombolysis. However, the use of thrombolysis with a standard dose in COVID-19 is recommended only for confirmed cases of pulmonary thromboembolism (PTE), preferably by computed tomography pulmonary angiography (CTPA), along with acute onset hypotension. In hemodynamically stable patients, the decision to thrombolyse must be individualized, taking several factors into account. However, successful use of Tissue plasminogen activator (tPA) in COVID-19-related severe hypoxia without confirmation of PTE on CTPA, obviating the need for mechanical ventilation, has also been reported.[2,5,6] Based on the positive outcome of these reports, we treated our patients with tPA as a last resort to salvage our patients.

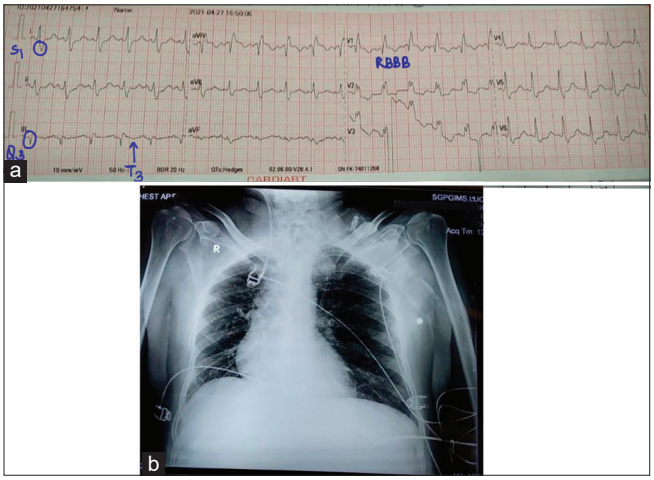


**Figure 1:** (a) Electrocardiogram showing a typical S1Q3T3 pattern along with recent-onset right bundle branch block, along with sinus tachycardia (heart rate: 136 bpm). (b) Chest X-ray representative of oligemic lung fields without consolidation

## METHODS

All six patients in this case series were COVID-19 reverse transcription-polymerase chain reaction positive and admitted to the ICU with severe hypoxia with an oligemic lung field without extensive consolidation on a chest X-ray (L-type phenotype). When patients developed sudden worsening of hypoxia, workup was performed to rule out common causes. Routine investigations, such as hemogram, serum pro-calcitonin to rule out hospital-acquired infection, inflammatory markers to rule out cytokine storm, a bedside chest X-ray to rule out pneumothorax and consolidation, electrocardiography (ECG), and echocardiography, were performed to look for evidence of pulmonary embolism. Right ventricular (RV) strain was defined by evidence of reduced pulmonary flow, an RV/left ventricular ratio >1, or evidence of RV dysfunction. Thromboelastography (TEG) of all patients was done. CTPA was not possible, as the patients were not stable enough to be shifted out of the ICU. We suspected micropulmonary thromboembolism in these patients with refractory hypoxia (PO2/FiO2 <100). Absolute contraindications for thrombolysis were absent in all patients. As tPA in such a setting is not the standard of care, informed consent was taken from a patient's relative. A low dose of tPA 0.4 mg/kg (approximately 30–50 mg) over 3 h was administered in all six patients. LMWH was discontinued for 24 h after tPA infusion. The Institute Ethics Committee approved the waiver of consent form (Ethics Cell No. 2021-27-IP-EXP-35).

## RESULTS

Case summaries are presented in Table 1. Two patients had acute onset hypotension along with worsening hypoxemia. One patient had hypotension along with an S1Q3T3 pattern along with a recent-onset right bundle branch block with right axis deviation on ECG [Figure 1]. TEG of case 3 showing a hypercoagulable state is shown in Figure 2. Echocardiography showed RV strain in four out of six patients. Deep vein thrombosis was not seen in any of the patients. D-dimer was elevated, platelet count was normal, and fibrinogen was more than 500 mg/d in all the patients. Oligemic lung fields suggested an L-type phenotype in all six patients. All six patients showed improvement in hypoxemia, as demonstrated by an improvement in the P/F ratio and reduction in the FiO2

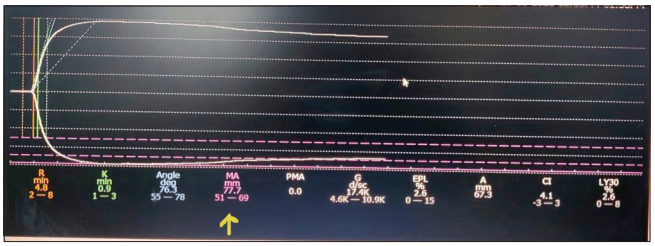

**Figure 2:** Thromboelastography of case 3 showing a hypercoagulable state.(Arrow)

**Table 1: Clinical features of patients**

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Age (years)/sex | 65/male | 55/male | 66/male | 42/male | 78/male | 60/male |
| Comorbidity | HTN | Generalized anxiety disorder | DM2 (U) | None | DM 2 (U) | DM, history of H1N1 ARDS in 2017 |
| CLD | No | No | No | No | No | No |
| CVA | No | No | No | No | No | No |
| RF requiring dialysis | No | No | No | No | No | No |
| Contraindications for thrombolysis | No | No | No | No | No | No |
| **Before tPA infusion initiation** | | | | | | |
| BMI (kg/m$^2$) | 26.7 | 28.9 | 29.1 | 27.3 | 28.8 | 26.9 |
| Intubated | No | Yes | Yes | No | No | Yes |
| P/F ratio | 80 | 112 | 100 | 134 | 110 | 120 |
| $PaCO_2$ mmHg | 39 | 35 | 41 | 38 | 40 | 38 |
| Respiratory rate (bpm) | 36 | 32 | 30 | 34 | 32 | 26 |
| Hypotension | No | No | Yes | No | No | No |
| Platelet (×10$^3$/mL) | 172 | 165 | 100 | 125 | 135 | 165 |
| D-dimer (mcg/ml) | 6245 | 7234 | 7790 | 7690 | 6930 | 3700 |
| FDP | Positive | Positive | Positive | Positive | Positive | Positive |
| Fibrinogen (mg/dL) | 545 | 617 | 561 | 608 | 729 | 618 |
| TEG | Hypercoagulable | Hypercoagulable | Hypercoagulable [Figure 2] | Hypercoagulable | Hypercoagulable | Hypercoagulable |
| Ferritin (ng/mL) | 2208 | 2156 | 1978 | 1756 | 1145 | 1450 |
| CRP (mg/L) | 145 | 101 | 96 | 125 | 70 | 125 |
| X-ray chest | OLF with BLLZI | OLF with BLLZI | OLF | OLF | OLF | OLF |
| ECG | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia, S1Q3T3, RAD [Figure 1] |
| Echocardiography | RV strain | RV strain | RV strain | WNL | WNL | RV strain |
| Doppler lower limb | No DVT | No DVT | No DVT | No DVT | No DVT | No DVT |
| Lung compliance | WNL | WNL | WNL | WNL | WNL | WNL |
| LMWH | Enoxaparin 60 mg BD | Enoxaparin 60 mg BD | Enoxaparin 60 mg BD | Enoxaparin 60 mg BD | Enoxaparin 60 mg BD | Enoxaparin 60 mg BD |
| tPA dose | 30 mg | 40 mg | 40 mg | 30 mg | 30 mg | 50 |
| ICU admission - tPA infusion day | 7 | 5 | 13 | 8 | 11 | 15 |
| Disease day 1 - tPA infusion day | 8 | 8 | 15 | 16 | 18 | 20 |
| **After tPA infusion** | | | | | | |
| P/F ratio 6 h after tPA | 100 | 150 | 180 | 150 | 150 | 175 |
| P/F ratio 24 h after tPA | 150 | 180 | 200 | 150 | 150 | 160 |
| P/F ratio 48 h after tPA | 180 | 180 | 150 | 100 | 150 | 150 |
| Vasopressor tapered | NA | NA | Yes | NA | NA | Yes |
| Bleeding complications | Mild hemoptysis | None | Mild GI bleed | Mild hematuria | None | None |
| Outcome | Expired | Expired | Expired | Expired | Expired | Expired |
| Interval tPA- death (day) | 7 | 5 | 13 | 7 | 5 | 5 |
| Cause of death | SS | SS, RH | RH, SS. | RH, SS | SS | SS |

UC: Uncontrolled, BLLZI: bilateral lower zone infiltrates, CLD: Chronic liver disease, DM: Diabetes mellitus, DM2: UC type 2 diabetes, DVT: Deep vein thrombosis, ICU: Intensive care unit, LMWH: Low molecular weight heparin, GI: gastrointestinal, NA: Not applicable, OLF: oligemic lung fields, P/F ratio: $PaO_2/FiO_2$ ratio, WNL: within normal limits, RAD: Right axis deviation, RH: Refractory hypoxemia, RF: Renal failure, RV: Right ventricle, SS: Septic shock, TEG: Thromboelastography, tPA: Tissue plasminogen activator, ARDS: Acute respiratory distress syndrome, BMI: Body mass index, FDP: Fibrin degradation product, ECG: Electrocardiography, CRP: C-Reactive Protein, HTN: Hypertension, CVA: Cerebrovascular Accident

requirement, which persisted for at least 48 h. The time from the start of infusion to death ranged from a minimum of 5 days to a maximum of 13 days. All patients terminally had evidence of sepsis and multiorgan failure.

## DISCUSSION

Two types of ARDS have been described in COVID-19: L type (low elastance) and H type (high elastance) [Figure 3].[1] The loss of lung perfusion and hypoxic vasoconstriction characterizes COVID-19-related L-type ARDS.[7] However, microthrombi obstructing pulmonary blood flow may also contribute to L-type ARDS pathology, where patients may have well-preserved lung mechanics and compliance. Improvement of oxygenation in all our patients suggests that microthrombi in pulmonary vasculature are a possible mechanism for refractory hypoxia and hypotension in these patients. Although patients finally succumbed to hospital-acquired sepsis, there was no mortality in the initial 4 days of tPA administration. The coexistence of multiple pathologies may also be responsible for final mortality. There might be polyphosphate-mediated fibrinolysis-resistant thick fibrin strands in the pulmonary circuit. The decision to administer tPA was late, as it is not a standard therapy in patients without confirmed PTE. Three patients

**Table 2: Summary of studies of tissue plasminogen activator in coronavirus disease 2019-related refractory hypoxia**

| Authors | Type of study | Intervention | Number of patients | Outcome and safety |
|---|---|---|---|---|
| Barret *et al*.[8] | Multicenter, Randomized Controlled Trial | Phase 1: Phase 1 (*n*=36): Control group (standard-of-care treatment) versus a tPA bolus+UFH infusion for 7 days<br>Phase 2 (*n*=14): tPA bolus+tPA infusion for 2 days+UFH infusion for 7 days | 50 | No significant difference in improvement in oxygenation or mortality. However, tPA infusion is safe |
| So *et al*.[9] | Multicentric Retrospective Cohort Observational study | Acute worsening of hypoxia<br>Acute hypotension requiring pressors<br>RV strain deep venous thrombosis<br>Increased dead space Vd | 57 | Improvement in oxygenation: 28/57 (47.4%)<br>Six patients discharged (Mortality: 89.6%)<br>Mild hemoptysis: 1<br>Major bleeding: 0 |
| Arachchillage *et al*.[10] | Case series | | 12 | Improvement in P/F ratio: 100%<br>Mortality: 43.6% |
| Barrett *et al*.[11] | Case series | | 5 | Improvement in P/F ratio: 100%<br>Transient: 40%<br>Persistent: 60% |
| Christie *et al*.[12] | Case series | | 5 | Improvement in P/F ratio: 100% |
| Poor *et al*.[6] | Case series | tPA 50 mg infusion over two hours followed by heparin drip | 4 | Improvement in P/F ratio 100%<br>Mortality 3/4 |
| Goyal *et al*.[5] | Case series | tPA infusion given early in the course of the disease, 50 mg over 3 h in 2 patients, 30 mg over 1 h in one patient | 3 | Improvement in P/F ratio: 100%<br>Mortality: 0<br>Bleeding: 0 |
| Wang *et al*.[13] | Case series | 25 mg intravenously over 2 h, followed by a 25 mg tPA infusion over the subsequent 22 h<br>Followed by heparin infusion | 3 | Transient improvement: 3<br>Durable: 1<br>Major or minor bleeding: 0 |
| Choudhury *et al*.[14] | A decision analysis Markov state simulation model | | 50,000 patients in each arm | Reduced mortality 47.6% versus71.0% in tPA and non-tPA group, respectively |
| Present study | Case series | tPA infusion 30-50 mg over 2-3 h | 6 | Improvement in P/F ratio: 100%<br>Mortality: 100%<br>Minor bleeding not requiring intervention: 3<br>Major bleeding: 0 |

P/F ratio: $PaO_2/FiO_2$ ratio, tPA: Tissue plasminogen activator, UFH: Unfractionated heparin, RV: Right ventricular, Vd: Ventilation, tPA: Tissue plasminogen activator

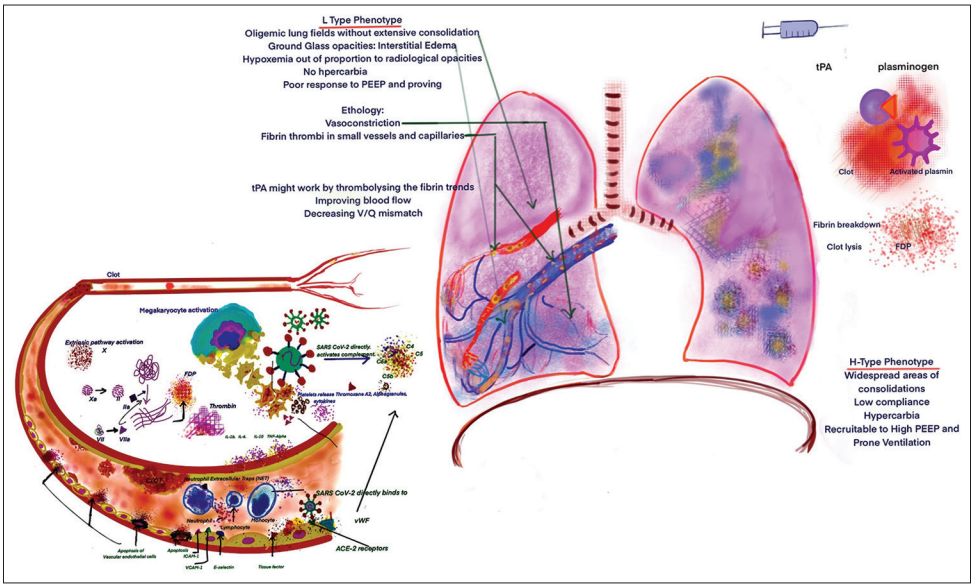


**Figure 3:** Severe acute respiratory syndrome-coronavirus-2 attaches to angiotensin-converting enzyme-2 receptors present on the vascular endothelium and damages it by direct infection, which leads to apoptosis and release of tissue factor and von Willebrand factor, activation of the complement pathway and activation of leucocytes, which lead to the release of interleukins. All these factors lead to the formation of fibrin from fibrinogen. Common phenotypes of acute respiratory distress syndrome in COVID-19 infection: L-type and H-type. Proposed mechanism of action of tissue plasminogen activator in the L-type phenotype

had bleeding complications: One patient had minor hemoptysis, one had gastrointestinal bleeding, and one had hematuria. However, all the cases were mild and could be managed conservatively. In our series, the decision to

start tPA ranged from 7 to 15 days of ICU admission, long enough to develop many other ICU-related complications. Therefore, maybe if we could identify our patients earlier, then that could have made a difference.

## Review of literature

A summary of all the studies on tPA in COVID-19 related hypoxia is presented in Table 2. The formation of microthrombi due to impaired fibrinolysis is a central mechanism in COVID-19-induced refractory hypoxia. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) attaches to angiotensin-converting enzyme-2 receptors present on the vascular endothelium and damages it by direct infection, which leads to apoptosis and release of tissue factor and von Willebrand factor.[7] This leads to activation of the complement pathway and activation of neutrophils, monocytes, and lymphocytes, which lead to the release of interleukin-l (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), and tissue necrosis factor-alpha. SARS-CoV-2 also directly activates platelets and megakaryocytes, which activates the extrinsic coagulation pathway, which leads to the formation of fibrin from fibrinogen. Fibrin degradation products are also released. Vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1, and E-selectin present in the endothelium play an important proinflammatory role. Therefore, a combination of endothelial damage and inflammation leads to a hypercoagulable state that leads to the generation of microthrombi.[15] The vast and unexplored spectrum of inflammation, endothelial injury, and pulmonary microcirculatory thrombosis contributes markedly to COVID-19-related ARDS.[16] Various conditions predispose COVID-19 patients to bleeding risk disseminated intravascular coagulation, thrombocytopenia, COVID-related hemophagocytosis, complications, and overuse of anticoagulants. Echocardiography, chest X-ray, routine tests, inflammatory markers, checking the settings of masks or ventilators are also indispensable parts of decision making.

A meta-analysis of 22 studies performed in animal models demonstrated a beneficial effect of thrombolysis in improving oxygenation and mortality.[17] Initial evidence for the use of tPA in COVID-19-related ARDS came from a short case series as a desperate attempt to do something for the patients. In a promising series, Goyal *et al*. demonstrated improvement and survival in a case series of three patients with worsening hypoxia with unconfirmed PTE. However, they used tPA early in the disease course.[5] Two other case series have used tPA in COVID-19-related ARDS in mechanically ventilated patients who had hypercarbia suggestive of increased dead space ventilation.[2,6]

A large multicentric study (57 patients) described findings similar to our series, where tPA was administered to patients with presumed but not confirmed PTE.[9] Improvement in oxygenation was seen in nearly half of the patients. However, mortality was high (89.5%). A recent randomized controlled trial comprising fifty patients demonstrated that administration of tPA followed by heparin improves the $PaO_2/FiO_2$ ratio at 48 h and is safe.[8] The trial could not show the clinical benefit of tPA in patients. However, it was underpowered to demonstrate this clinical benefit due to the small number of patients.

The dose and route of administration of tPA are also important issues. Plasma clearance of tPA is approximately 8 min, and the plasma half-life is approximately 88 min.[18] The most common route of administration is intravenous bolus infused over 2–3 h. The MOPETT trial demonstrated that a lower dose of tPA decreases bleeding complications without compromising efficacy.[19]

The safety of tPA is also an essential issue, as fear of bleeding prevents clinicians from using it at an appropriate time. Almost all of the case series and trials have demonstrated the safety of tPA in terms of a major bleed. However, we avoided femoral arterial puncture for 48 h after stopping tPA infusion. Absolute contraindications to tPA are a prior history of intracranial hemorrhage, a cerebral vascular lesion, malignant intracranial neoplasm, ischemic stroke within the preceding 3 months, suspected aortic dissection, active bleeding from any other site or bleeding diathesis, and significant closed-head trauma or facial trauma within the prior 3 months.

One ongoing trial is also assessing the role of nebulized recombinant tPA in mechanically ventilated patients and those on noninvasive ventilation and high-flow oxygen.

## Declaration of patient consent

The Institute Ethics Committee approved the waiver of the consent form (Ethics Cell No. 2021-27-IP-EXP-35).

## Ethical approval

The Institute Ethics Committee approved the waiver of the consent form (Ethics Cell No. 2021-27-IP-EXP-35).

## Financial Support and Sponsorship:

Nil.

## Conflicts of Interest

There are no conflicts of interest.

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