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## Case Report

## Recombinant tissue plasminogen activator treatment for COVID-19 associated ARDS and acute cor pulmonale



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## ABSTRACT

Existing literature highlights the fact that patients with COVID-19 exhibit alterations in the coagulation process and are associated with respiratory and cardiovascular diseases, including acute respiratory distress syndrome and acute cor pulmonale. In this report, we describe the effects of systemic thrombolysis on acute cor pulmonale in a patient suffering from COVID-19. We demonstrated that systemic thrombolysis successfully improved the hemodynamics of our patient and resulted in a prominent reduction in hypercapnia, alveolar dead space, and ventilatory ratio.

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## Introduction

Acute cor pulmonale (ACP) is characterized by an unexpected rise in pulmonary vascular resistance and is closely associated with acute respiratory distress syndrome (ARDS) (Jardin and Vieillard-Baron, 2009; Biswas, 2016). We have all witnessed the pandemic spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; research has shown that some patients suffering from this disease (coronavirus disease 2019; COVID-19) have developed ARDS (Wang et al., 2020). Interestingly, Creel-Bulos et al. reported the development of ACP in patients with severe forms of COVID-19 (Creel-Bulos et al., 2020). It has also been suggested that alterations in the coagulation process and augmented levels of D-dimer are important attributes of the form of pneumonia that develops in patients infected with SARS-CoV-2 (Tang et al., 2020). Recent study has also revealed that tissue plasminogen activator can be used as a treatment in patients with COVID-19 associated ARDS and provides some initial and transient improvements (Wang et al., 2020). In this report, we describe the effects of systemic thrombolysis on ACP in a patient suffering from COVID-19.

## Case presentation

A 67-year-old male non-smoker was admitted to the emergency department of our hospital at the end of April 2020. Initial symptoms included a dry cough, high-grade fever (39.4 °C), and myalgia; subsequently, the patient went on to develop progressive dyspnea. Chest computed tomography (CT) showed diffuse bilateral ground glass opacities that predominantly involved the lower lobes. The patient was obese and suffering from arterial hypertension. He was receiving a range of treatments, including oral enalapril, atenolol and rosuvastatin. COVID-19 infection was confirmed by the positive detection of SARS-CoV-2 RNA from a nasopharyngeal swab.

On admission, the patient was severely hypoxemic (SpO<sub>2</sub>: 76% while breathing room air). He was started on a nasal cannula (6 LPM), but was then placed on non-invasive mask ventilation (continuous positive airway pressure (CPAP) = 11 cmH<sub>2</sub>O, with a fraction of inspired oxygen (FiO<sub>2</sub>) of 60%). However due to the progression of hypoxemic respiratory failure, the patient was intubated and placed on mechanical ventilation (pressure control ventilation (PCV) with a positive end-expiratory pressure (PEEP) of 12 cmH<sub>2</sub>O and a FiO<sub>2</sub> of 60–80%).

The patient developed ACP and exhibited increased systolic pulmonary arterial pressure (SPAP), high levels of D-dimer, obvious hypercapnia, high alveolar dead space, and a high ventilatory ratio with close to normal static compliance (Table 1). CT pulmonary angiograms and bilateral lower limb Doppler scans did not show any signs of pulmonary embolism or deep vein thrombosis. The

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**Table 1**

The effects of recombinant tissue plasminogen activator treatment on echocardiographic parameters, respiratory mechanics, blood parameters, and ventilation status.

Echocardiography	Before	After
SPAP, mmHg	52	40
RV basal diameter, mm	37	36
RV midlevel diameter, mm	35	33
RV end-diastolic area, cm <sup>2</sup>	22	20
RA end-systolic area, cm <sup>2</sup>	17	16.4
TAPSE, mm	18	20
<b>Respiratory mechanics</b>		
Rrs, cmH <sub>2</sub> O/L/s	16	16
Static respiratory system compliance, mL/cmH <sub>2</sub> O	50	58
R/I ratio	0.38	0.39
Driving pressure, cmH <sub>2</sub> O	13	12
<b>Blood gas analysis</b>		
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	116	170
PaCO <sub>2</sub> , mmHg	70	39
pH	7.38	7.43
HCO <sub>3</sub> <sup>-</sup> , mEq/L	31.6	27.6
<b>Ventilation status</b>		
Alveolar dead space, mL	204.3	53.8
Ventilatory ratio	3.73	2.05
<b>Blood analysis</b>		
D-dimers, mg/L	53.6	56.3
CRP, mg/L	68	19
Ferritin, ng/mL	2142	1254
ALT, U/L	133	81
AST, U/L	127	60
LDH, U/L	2540	1643

**Abbreviations:** SPAP = systolic pulmonary arterial pressure, RA = right atrium, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion, Rrs = respiratory system resistance, R/I = recruitment-to-inflation, PaO<sub>2</sub> = partial pressure of oxygen, FiO<sub>2</sub> = fraction of inspired oxygen, PaCO<sub>2</sub> = partial pressure of carbon dioxide, CRP = C-reactive protein, ALT = alanine transaminase, AST = aspartate transaminase, LDH = lactate dehydrogenase, ventilatory ratio = minute ventilation (mL/min) × PaCO<sub>2</sub> (mmHg)/(predicted body weight × 100 × 37.5).

patient was treated with hydroxychloroquine, azithromycin, ceftriaxone, enoxaparin (prophylactic dose), and tocilizumab (800 mg intravenously). Furthermore, we treated the patient with off-label recombinant tissue plasminogen activator (rtPA; approved by the local medical multidisciplinary consilium). rtPA was applied at a dose of 25 mg over a period of two hours; then, 25 mg of rtPA was infused over the next 22 h (Wang et al., 2020). During rtPA treatment, the body temperature of the patient was stable (approximately 37 °C). Blood glucose levels were measured several times each day. On the day of the rtPA administration, and thereafter, the blood glucose levels were in the range of 5.2–6.9 mmol/L. Following rtPA treatment, there was a strong reduction in SPAP, hypercapnia, alveolar dead space, and ventilatory ratio, and a slight increase in static compliance (Table 1). In addition, there were improvements in the oxygenation status of the patient (Table 1). Interestingly, rtPA treatment also resulted in the reduction of various parameters in the blood, including ferritin and several markers of liver status, tissue damage, and inflammation (Table 1). Unfortunately, the patient passed away on 14<sup>th</sup> May 2020 due to ventilator-associated pneumonia and septic shock (*Acinetobacter baumannii*).

## Discussion and conclusion

COVID-19 is characterized by changes in the coagulation process, reduced fibrinolysis, and microvascular thrombosis of the lung vessels; this disease is also associated with ARDS and ACP (Wang et al., 2020; Creel-Bulos et al., 2020; Tang et al., 2020; Kruse et al., 2020). A markedly reduced level of fibrinolysis plays an important role in the hypercoagulable state and thromboembolic risk in patients with COVID-19 (Kruse et al., 2020). This process

may underline the possible use of fibrinolytic therapy in patients with ARDS due to COVID-19. Recent publications suggested the application of rtPA as a potential treatment option for patients with COVID-19 associated ARDS (Moore et al., 2020; Orfanos et al., 2020). Our COVID-19 patient developed ACP and had high values of ferritin, C-reactive protein, hypercapnia, and alveolar dead space; all of these parameters were reduced after rtPA treatment. In the line with our findings, Papamichalis et al. reported reduced levels of ferritin and C-reactive protein following the administration of rtPA and tocilizumab (Papamichalis et al., 2020). Hypercapnia has also been linked with the development of ACP and is thought to represent one of the factors responsible for vasoconstriction and the augmentation of pulmonary arterial pressure (Jardin and Vieillard-Baron, 2009; Biswas, 2016; Boissier et al., 2013). Furthermore, in our patient, rtPA treatment resulted in the reduction of ventilatory ratio and an improvement in oxygenation status; this concurs with another article that was published recently (Price et al., 2020).

Although the CT pulmonary angiogram scan did not show signs of pulmonary embolism, there is still a possibility that an obstruction existed in the small vessels and may have led to the development of ACP. The respiratory pathophysiology of COVID-19 is very complex; it has been suggested that inflammatory diffuse micro-thrombosis contributes to severe hypoxemia (Ackermann et al., 2020; Vasques et al., 2020). In cases of ARDS that are associated with COVID-19, it is possible that severe micro-thrombosis may be viewed as a unique phenotype that is characterized by elevated D-dimers levels, an increased fraction of dead space, hypercapnia, and pulmonary hypertension.

Importantly, the patient described in our study had certain comorbidities, including obesity and hypertension. Therefore, one may ask whether the effects of rtPA could have been more prominent if the patient did not have such comorbidities. Future studies should focus on this interesting question and attempt to reveal the beneficial effects of rtPA in patients with different health conditions.

Overall, our study showed that systemic thrombolysis in our patient suffering from COVID-19 associated with ARDS and ACP resulted in improved hemodynamics and reduced hypercapnia, alveolar dead space, and ventilatory ratio.

## Funding source

None.

## Conflicts of interest

None declared.

## Ethics approval and consent to participate

Written informed consent was obtained from the patient's next of kin.

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