

Acute pulmonary embolism and systemic thrombolysis in the era of COVID-19 global pandemic 2020: a case series of seven patients admitted to a regional hospital in the French epidemic cluster

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Background

The novel Coronavirus [named severe acute respiratory syndrome-related coronavirus 2 (SARS CoV-2)] was associated with the development of acute respiratory distress syndrome (ARDS), which required mechanical ventilation in a high percentage of critically ill patients. Recent studies have highlighted a state of hypercoagulability in patients with SARS-CoV-2, leading to an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). The low proportion of PE-associated to DVT in COVID-19 patients may suggest that they have pulmonary thrombosis rather than embolism. There is no guideline recommendation on the treatment of massive PE in COVID-19 patients suffering from ARDS, without cardiogenic shock.

Case summary

We described a series of seven SARS-COV-2 patients diagnosed with PE, in our institution, who underwent the use of systemic thrombolysis (recombinant tissue plasminogen activator) according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min.

Discussion

According to the European Society of Cardiology (ESC) severity scale, three patients had high-risk PE and four had intermediate high-risk PE. Systemic thrombolysis was found to be associated with a reduction of the Brescia-COVID Respiratory Severity Scale in five patients, recording a reduction from 3 to 1 in 2/5 patients, and from 3 to 2 in 3/5 patients. Furthermore, 3/5 patients had an initial improvement of their alveolar partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ratio ranging from a 19% (Patient 3) to a 156% improvement (Patient 6). It was also associated with a decrease of the right ventricular (RV) dysfunction and the RV/left ventricular ratio 24 h later. No major bleeding events occurred after the thrombolysis, but the overall mortality after performing systemic thrombolysis was up to 3/7 patients.

Conclusion

Despite the low level of knowledge about the underlying pathophysiology of the COVID-19 ARDS, venous thromboembolic events, and the microvascular thrombosis, our findings suggest that in the treatment of PE with

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RV failure in patients with COVID-19 suffering from ARDS, without cardiogenic shock, systemic thrombolysis should be considered.

Keywords

COVID-19 • Pulmonary embolism • Thrombolysis • Case report

Learning points

- The inability to identify and accurately manage pulmonary embolism (PE) in patients admitted with COVID-19 acute respiratory distress syndrome (ARDS), could worsen the short-term prognosis of these patients.
- Systemic thrombolysis may be considered in COVID-19 patients suffering from ARDS who develop PE with right ventricular failure without cardiogenic shock.
- Possible entanglement of pulmonary microvascular thrombosis in COVID-19-related ARDS.

Introduction

The 2020 world pandemic due to a novel Coronavirus [named severe acute respiratory syndrome-related coronavirus 2 (SARS CoV-2)], that started in Wuhan (China), was associated with the development of acute respiratory distress syndrome (ARDS) and required mechanical ventilation in a high percentage of critically ill patients. The pathophysiology of ARDS results from an acute systemic inflammation that leads to a cytokine storm. The increase in proinflammatory cytokines within the lung, leads to the recruitment of leucocytes, further propagating the local inflammatory response and conducting to an abnormal gas exchange.

Recent studies have highlighted the changes in blood coagulation of patients with SARS-CoV-2.¹ This state of hypercoagulability leads to an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE). The incidence of PE in COVID patients is not clearly established. Despite systematic thrombosis prophylaxis with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) according to the current guidelines.^{2,3} Some series have shown that the incidence of venous thromboembolic events in COVID-19 patients in intensive care unit (ICU) reached 27%.⁴

Nevertheless, the low proportion of PE-associated with DVT in COVID-19 patients may suggest that they have pulmonary thrombosis rather than embolism.⁵

We report a series of seven COVID-19 patients with PE in our institution that required the use of systemic thrombolysis, the molecule used was the recombinant tissue plasminogen activator (rtPA).

Case presentation

Patient 1

A 40-year-old man, with no medical history, was admitted to the Emergency Unit for dyspnoea. He described that he had suffered from a progressive dyspnoea on exertion followed by a flu-like syndrome during the previous 15 days.

On admission, the patient was found to have a body temperature of 38°C, an oxygen saturation of 75% in breathing ambient air, and a tachypnoea at 32 cycles/min.

In the situation of this severe dyspnoea situation, an oxygen therapy was started at 6 L/min and a blood test was performed.

The major biological finding were D-dimer >20 000 ng/mL, and troponin at 0.084 ng/mL. SARS CoV-2 was detected by RT-PCR from nasopharynx.

According to the blood test results, a computed tomography (CT) pulmonary angiography (CTPA) scan was performed. It showed a massive PE with an acute pulmonary heart and multifocal peripheral ground glass opacities bilaterally evocating a COVID pneumonia.

The paraclinical investigations were completed by a transthoracic echography (TTE) that showed an acute pulmonary heart with right ventricular (RV)/left ventricular (LV) ratio at 1.8, an abnormal septum motion, a RV dysfunction and there was no visible thrombus.

The patient was transferred to ICU, but after a few hours, he developed respiratory distress underlying non-invasive ventilation 70% FiO₂ with tachypnoea and hypoxaemia without haemodynamic failure.

The decision was made to start a systemic thrombolysis using rtPA according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min followed by UFH anticoagulation for at least 48 h.

The patient's clinical evolution was favourable with an improvement in his respiratory status and a decrease in his respiratory rate. The oxygen requirement was only 4 L/min 24 h post-thrombolysis.

Follow up: The oxygen requirement of the patient was decreased progressively and he was in breathing ambient air 48 h after thrombolysis. The patient was discharged from hospital on Day 6, under Rivaroxaban 15 mg twice a day and then at Day 22, Rivaroxaban 20 mg once a day for at least 6 months.

Patient 2

A 53-year-old woman, active smoker, with a history of dysthyroidism, was admitted to the Emergency Unit with chest pain and dyspnoea. She complained of having had a fever, a cough, and had suffered from myalgia and diarrhoea for the previous 15 days.

On admission, the patient was suffering from a lateral chest pain. On auscultation, crackles were audible up to the mid zone on both sides. Her oxygen saturation in breathing ambient air was up to 85%.

In the presence of lateral chest pain, a blood test and an electrocardiogram (ECG) were performed, that showed D-dimer >20 000 ng/mL, and a sinus tachycardia at 105 b.p.m., with s1q3T3 pattern, and T-wave inversions in the right precordial leads.

Timeline

Patient 1: Male, 40 years old

Day 1: Flu-like symptoms.

Day 15: Respiratory distress. Oxygen saturation of 75% in breathing ambient air. Diagnosis of pulmonary embolism (PE) and admission to intensive care unit (ICU).

Day 16: Respiratory distress underlying non-invasive ventilation 70% FiO₂ with tachypnoea and hypoxaemia without haemodynamic failure. Systemic thrombolysis.

Day 17: Oxygen requirement was only 4 L/min 24 h after thrombolysis.

Day 18: Ambient air.

Day 21: Discharged from hospital.

Patient 2: Female, 53 years old

Day 1: Fever, cough, myalgia, and diarrhoea.

Day 15: Saturation at 85% in breathing ambient air. Diagnosis of PE and admission to ICU.

Day 16: Respiratory distress with oxygen saturation of 85% under 15 L/min with tachypnoea, but no haemodynamic failure. Systemic thrombolysis.

Day 18: Ambient air.

Day 24: Discharged from hospital.

Patient 3: Male, 58 years old

Day 1: Cough with fever.

Day 21: Saturation at 94% in breathing ambient air. Diagnosis of PE and admission to ICU.

Day 23: Respiratory distress, with oxygen saturation of 94% under 15 L/min and tachypnoea (45 cycles/min).

Day 24: Oxygen requirement was only 4 L/min 24 h after thrombolysis.

Day 35: Discharged from hospital.

Patient 4: Male, 67 years old

Day 1: Non-producing cough, fever and a worsening dyspnoea.

Day 10: SARS CoV-2 was detected by RT-PCR from nasopharynx. Acute respiratory distress syndrome (ARDS) that required mechanical ventilation and transfer to ICU.

Day 23: Respiratory distress, tachypnoea, and circulatory collapse with cardiogenic shock. Diagnosis of PE.

Day 24: Deceased.

Patient 5: Male, 66 years old

Day 1: Flu-like symptoms.

Day 30: Respiratory distress. Saturation at 78% in breathing air. Diagnosis of PE, systemic thrombolysis and admission to ICU.

Day 32: Deceased.

Patient 6: Female, 38 years old

Day 1: Medio-thoracic chest pain without irradiation, followed by a severe dyspnoea.

Sudden cardiac arrest. PE diagnosis. Systemic thrombolysis.

Day 3: Extubation.

Day 12: Discharged from hospital.

Patient 7: Male, 68 years old

Day 1: Respiratory distress. Oxygen saturation between 80% and 85% on ambient air. PCR-RT from nasopharynx was positive. Transferred to ICU with ARDS.

Day 6: Respiratory distress, circulatory collapse with cardiogenic shock. Diagnosis of PE. Systemic thrombolysis.

Day 8: Transferred to Strasbourg Regional Hospital.

Day 12: Put under venoarterial extracorporeal membrane oxygenation.

Day 19: Deceased.

The S1Q3T3 pattern shows the presence of an S-wave in lead I (indicating a rightward shift of QRS axis) with Q-wave and T inversion in lead III ([Figure 1](#)).⁶

The major suspicion of PE led to a CTPA that confirmed the diagnosis and showed pulmonary lesions of COVID-19 infection.

The patient was transferred to ICU, and a TTE was done on arrival. The echography showed an RV/LV ratio of 2, an abnormal septum

motion with an elevation of the RV systolic pressure (RVSP) at 68 mmHg, atrial septal aneurysm with patent foramen ovale.

Intravenous UFH was started with a target between 2 and 3 times the control activated partial thromboplastin time (aPTT).

Twenty-four hours later, the patient presented with respiratory distress and oxygen saturation of 85% under 15 L/min O₂ with tachypnoea, but without haemodynamic failure.

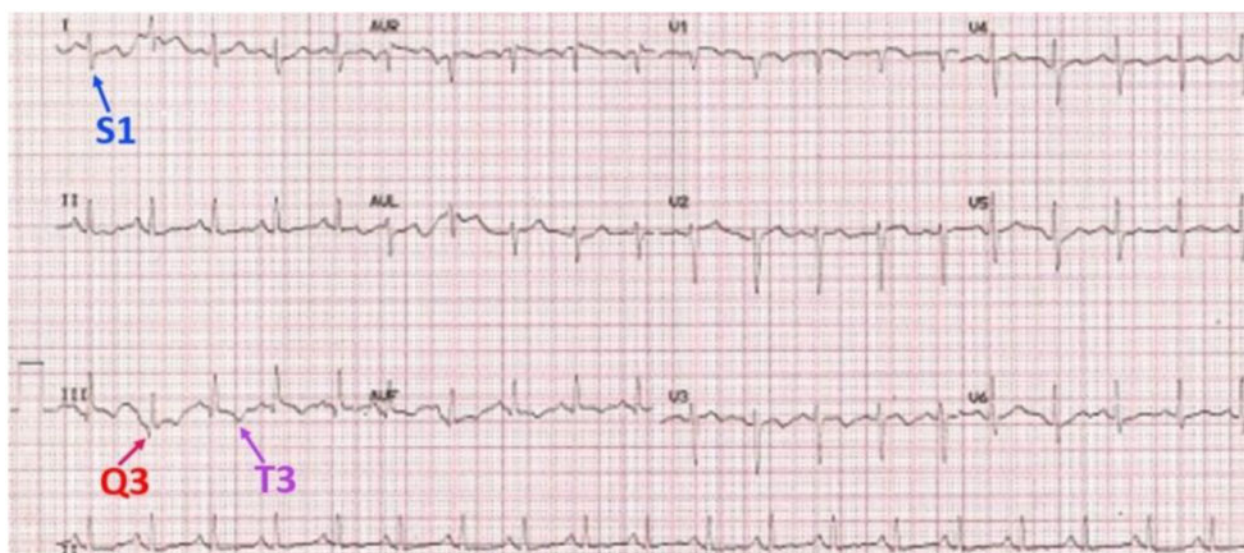


Figure 1 Electrocardiogram showing a S1Q3T3 pattern.



Figure 2 Pulmonary computed tomography angiography image in axial plane showing a proximal bilateral pulmonary embolism.

A systemic thrombolysis was performed according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min.

Follow-up: Favourable clinical evolution and on breathing ambient air 48 h later. She was discharged from hospital on Day 9 under Rivaroxaban 15 mg twice a day and then at Day 22, Rivaroxaban 20 mg once a day for at least 6 months.

Patient 3

A 58-year-old man was admitted to the Emergency Unit with a cough and fever that had evolved over the previous 3 weeks.

The ECG showed a sinus tachycardia of 100 b.p.m., with a S1Q3T3 pattern.

A CTPA was performed and showed a massive PE with acute right heart signs, and pulmonary lesions of COVID-19 infection.

In this patient, the first SARS CoV-2 RT-PCR from nasopharynx was negative, but the second one 24 h later was positive. After the

CTPA, an intravenous UFH was started with a target between 2 and 3 times the control aPTT, and the patient was transferred to ICU.

The TTE on arrival, showed an RV/LV ratio of 2, abnormal septum motion, RV dysfunction with an elevation of the RVSP at 60 mmHg. A thrombus was visible in the right pulmonary artery.

Two days after his admission to ICU, he presented with severe respiratory distress, an oxygen saturation of 94% under 15 L/min and a tachypnoea (45 cycles/min).

A systemic thrombolysis was started using rtPA according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min. After 24 h, the patient was under 4 L of oxygen per minute.

Follow up: Patient was discharged from hospital on Day 14 under Rivaroxaban 15 mg twice a day and then at Day 22, Rivaroxaban 20 mg once a day for at least 6 months. The TTE was controlled after 1 month and did not show any abnormalities.

Patient 4

A 67-year-old man with no medical history was admitted to the Emergency Unit.

He complained of a 10-day history of non-productive cough, fever, and a worsening dyspnoea.

SARS CoV-2 was detected by RT-PCR from nasopharynx.

Rapidly, the patient developed an ARDS, which required mechanical ventilation and transfer to ICU.

In ICU, the patient was under LMWH preventive thromboprophylaxis with Enoxaparine 8000 UI once a day. His clinical status was improving but 13 days after admission, he presented with severe dyspnoea, respiratory distress, tachypnoea, and circulatory collapse with cardiogenic shock.

The TEE showed an RV/LV ratio at 1.5, an abnormal septum motion, an RV dysfunction with no visible thrombus.



Figure 3 Chest computed tomography on lung window in axial plane showing COVID 19 lesions and pulmonary embolism.

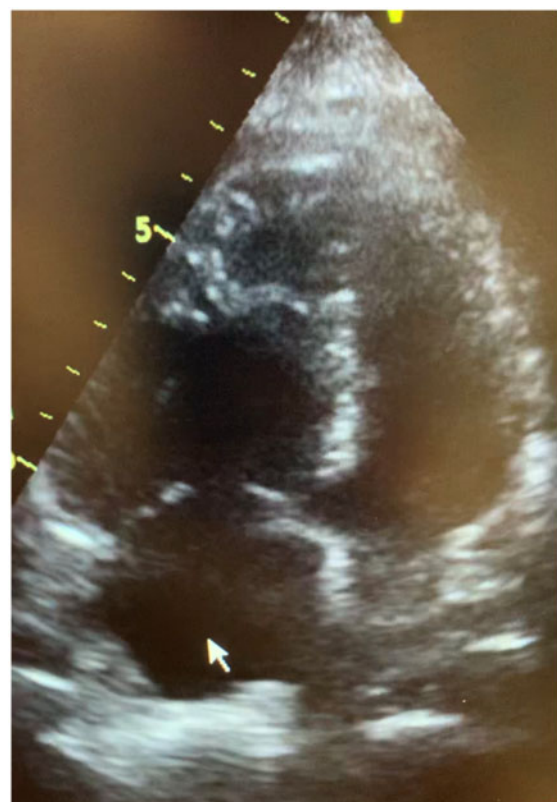


Figure 4 Echocardiography showing a right ventricular dilatation in apical four-chamber right ventricle focused view of a patient with an acute pulmonary embolism.

A CTPA was performed that showed the massive PE and pulmonary lesions of COVID-19 infection.

A systemic thrombolysis was decided according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min.

Follow up: Despite the use of vasopressor drugs, and a discussion of venoarterial extracorporeal membrane oxygenation (ECMO) the patient died 24 h later.



Figure 5 Echocardiography with a visible thrombus at the bifurcation of the main pulmonary artery.

Patient 5

A 65-year-old man, with a past medical history of epilepsy.

He complained of having had flu-like symptoms for the previous month, with an aggravation of the dyspnoea that led him to call the emergency unit. On arrival of the paramedical unit, the patient had an oxygen saturation of 78% in breathing air, with a tachypnoea of 40 cycles/min. The patient was put on oxygen and transported to the Emergency Unit. On admission, the patient was in respiratory distress, with an oxygen saturation of 97% under 15 L/min and tachypnoea (42 cycles/min) but no haemodynamic failure.

The ECG showed sinus tachycardia of 100 b.p.m., S1Q3T3 pattern, and incomplete right bundle branch block.

CTPA confirmed a massive PE and pulmonary lesions of COVID-19 infection (Figures 2 and 3).

The first SARS CoV-2 RT-PCR from nasopharynx was negative, but the second one 48 h later was positive.

The TTE showed an RV/LV ratio >4.5 , an abnormal septum motion, an RV dysfunction with an elevation of the RVSP at 60 mmHg, and a thrombus in the right atrium.

In this context, the decision was made to start a systemic thrombolysis according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min and the patient was transferred to ICU.

Table 1 Demographic, clinical, and paraclinical characteristics

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Demographic characteristics							
Age (years)	40	53	58	67	66	38	68
Sex	Male	Female	Male	Male	Male	Female	Male
BMI (kg/m ²)	28.36	32.01	25.51	24.16	31.5	30.8	23.11
Initial findings							
Medical history	No background	Dysthyroidism, Active smoker	Appendicectomy	No background	Epilepsy	Post-traumatic PE, Paraplegic	Stroke, Patent foramen ovale
VTE background	None	None	None	None	None	PE with major provocation factor (surgery)	None
VTE major provocation factor prior to admission	None	None	None	None	None	None	None
SARS-Cov2 pneumonia diagnosis							
PCR SARS-Cov2	Positive	Negative	Positive	Positive	Positive	Negative	Positive
Diagnostic on CT scan	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Diffuse parenchymal lung injury (%)	>75	50–75	NA	>75	>75	<25	>75
PE characteristics							
PE diagnostic delay ^a (days)	15	15	21	23	28	15	20
sPESI score at event	2	1	1	1	2	2	1
PE severity ^b	Intermediate–high	Intermediate–high	Intermediate–high	High-risk	Intermediate–high	High-risk	High-risk
Anticoagulation prior to PE diagnosis	None	None	None	Preventive LMWH	None	None	Preventive LMWH
Systemic thrombolysis							
BP at thrombolysis (mmHg)	131/89	140/87	123/76	80/65	110/90	Non-measurable	75/55
Symptoms requiring thrombolysis	Respiratory distress underlying non-invasive ventilation	Respiratory distress with saturation at 85% under 15 L/min	2 days after admission in ICU, brutal respiratory distress, with saturation at 94% under 15 L/min	13 days after admission in ICU, brutal respiratory distress, collapse with cardiogenic shock	Respiratory distress, saturation at 97% under 15 L/min, tachypnoea (42 cycles/min)	Sudden cardiac arrest No flow 0 min Low flow 30 min	5 days after admission in ICU, respiratory distress, collapse with cardiogenic shock
	70% FiO ₂ , Tachypnoea, Hypoxaemia, No haemodynamic failure	O ₂ , Tachypnoea, hypoxaemia, No haemodynamic failure	94% under 15 L/min, Tachypnoea (40 cycles/min)	collapse with cardiogenic shock	No haemodynamic failure		
Fibrinolytic agent	rtPA	rtPA	rtPA	rtPA	rtPA	rtPA	rtPA
Brescia-COVID Respiratory Severity Scale ^c before thrombolysis	3	3	3	3	3	3	3
Brescia-COVID Respiratory Severity Scale at H + 24 thrombolysis	1	1	2	NA	2	NA	2
Laboratory findings							
PaO ₂ /FiO ₂ at thrombolysis	180	146	158	85	227	139	135

Continued

Table 1 Continued

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
PaO ₂ /FIO ₂ at H + 24 thrombolysis	271	NA	188	NA	198	357	125
Haemoglobin (g/dL) before thrombolysis	13.9	9.9	13.6	11.2	13.5	12.3	10.3
Haemoglobin (g/dL) at H24 after thrombolysis	10.8	9.7	12.4	NA	12.1	11.4	9.6
D-dimer (ng/mL)	>20 000	2352	>20 000	15 000	NA	NA	702
Troponin I at admission (ng/mL)	0.084	2.5	NA (HST I at 35)	<0.010	NA (HST I at 346)	0.060	0.013
NT-proBNP at admission (ng/L)	2630	4625	624	125	2104	2971	963
Creatinin (micromole/L)	78	91	93	65	120	71	87
eGFR (mL/min/1.73m ²)	107	63	77	96	54	93	78
High-sensitivity C-reactive protein (mg/L)	97	11	155	55	133	52	101
Activated partial-thromboplastin time (s)	31	30.3	NA	33	36.8	50	35.8
Prothrombin time (%)	91	85	NA	101	79	60	106
Antiphospholipid antibodies	LupusAnticoagulant+	Negative	Negative	Anti-β ₂ glycoprotein I antibodies + Anti-cardiolipin Ig anti-bodies +	NA	Negative	NA
Echocardiography findings							
Before thrombolysis							
	RV/LV = 1.8 abnormal septum motion	RV/LV = 2 abnormal septum motion	RV/LV = 2 abnormal septum motion	RV/LV = 1.5 abnormal septum motion	RV/LV > 4.5 abnormal septum motion	RV/LV > 1.3 Mc Connell sign	RV/LV > 1 Abnormal septum motion RV dysfunction
	RV dysfunction	RVSP = 68 mmHg	RV dysfunction	RV dysfunction	RV dysfunction	Thrombus in pulmonary artery	
	No thrombus visualized	ASA with PFO	Thrombus in right pulmonary artery	No thrombus visualized	RVSP = 60 mmHg	RVSP = 55 mmHg	
After H + 24 thrombolysis							
	RV/LV < 1	RV/LV < 1	RV/LV = 1.5	NA	NA	RV/LV < 1	RV dilatation
	No RV dysfunction	No RV dysfunction	Abnormal septum motion			No RV dysfunction	No RV dysfunction
	RVSP = 56 mmHg	RVSP = 45 mmHg	RVSP = 50 mmHg			RVSP = 29 mmHg	RVSP = 58 mmHg
DVT	Yes	Yes	No	NA	Yes	No	Yes
Follow-up							
Death	No	No	No	Yes	Yes	No	Yes
Hospitalization length	6 days	9 days	14 days	15 days	2 days	11 days	19 days
Anticoagulation treatment at discharge	Rivaroxaban	Rivaroxaban	Rivaroxaban	None	None	Rivaroxaban	None

^aDelay between the symptoms and the PE diagnosis.^bAccording to ESC guidelines.^cBrescia-COVID Respiratory Severity Scale.⁶

ASA, atrial septal aneurysm; BP, blood pressure; BMI, body mass index; CT, computerized tomography; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; kg, kilograms; FIO₂, inspired fraction of oxygen; HST I, high-sensitive Troponin I; ICU, intensive care unit; LMWH, low molecular weight heparin; LV, left ventricular; NA, not available; NT-pro BNP, N-terminal pro brain natriuretic peptide; PaO₂, alveolar partial pressure of oxygen; PCR, polymerase chain reaction; PE, pulmonary embolism; PFO, patent foramen ovale; RV, right ventricular; RVSP, right ventricular systolic pressure; sPESI, simplified pulmonary embolism severity index; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; UFH, unfractionated heparin; VTE, venous thromboembolic events.

Follow-up: The patient presented a clinical improvement 24 h after the thrombolysis, but died 48 h later, from a refractory sudden cardiac arrest.

Patient 6

A 38-year-old woman, with a past medical history post-traumatic PE.

She complained of a medio-thoracic chest pain, followed by a severe dyspnoea. On the arrival of the Emergency Unit, the patient was conscious but then had a sudden cardiac arrest, no-flow 0 min and low-flow 30 min. She was intubated, given cardiopulmonary resuscitation and transferred to the Emergency Room.

At arrival, the TTE found an RV dysfunction and a thrombus in the pulmonary arteries (Figures 4 and 5).

A CTPA scan confirmed the massive PE and showed pulmonary lesions of COVID-19.

A systemic thrombolysis was performed according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min and the patient was transferred to ICU.

Follow up: A favourable clinical evolution and was extubated 2 days after.

The transthoracic cardiac echography was controlled 7 days after, showing no abnormalities.

She was discharged from hospital at Day 11, under Rivaroxaban 15 mg twice a day and then at Day 22, Rivaroxaban 20 mg once a day for at least 6 months.

Patient 7

A 68-year-old man, with a medical history of stroke, was admitted to the Emergency Unit with respiratory distress. The physical examination, found a tachypnoea, an oxygen saturation between 80% and 85% in ambient air and a body temperature of 38.5°C. In this dyspnoea situation, a blood test and a CT scan were performed.

The laboratory findings were a troponin at 0.013 ng/mL, D-dimer at 700 ng/mL, and a positive PCR-RT from nasopharynx.

The CT scan found diffuse pulmonary lesions of COVID-19.

The patient was transferred to ICU for ARDS. An antibiotherapy with Rovamycine and Cefotaxime was started, and the patient was under LMWH preventive thromboprophylaxis with Enoxaparine 7000 UI once a day.

Five days after admission, he developed respiratory distress, circulatory collapse with cardiogenic shock.

The TTE showed an acute right dysfunction with RV/LV ratio >1, an abnormal septum motion and an RV dysfunction.

A systemic thrombolysis was decided according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min.

Follow-up: Though there was an improvement of echography criteria, the clinical state of the patient worsened. He was transferred to Strasbourg regional hospital and put on venoarterial ECMO. Unfortunately, the patient died after 7 days under ECMO.

Results and discussion

Our population was composed of 71% male, of an average age of 55 years, a mean body mass index of 27.9 kg/m², and none had major venous thromboembolic events provocation factors except the relative immobilization secondary to the COVID-19 disease. All the detailed characteristics appear in Table 1.

Patients were treated with systemic thrombolysis using rtPA according to the standard protocol of 10 mg over 15 min, then 90 mg over 120 min followed by UFH anticoagulation.

The current European Society of Cardiology (ESC) guidelines suggest the use of systemic thrombolysis in patients with high-risk PE, defined mainly by the presence of cardiogenic shock.⁷ In our case-series, 4/7 (57%) patients did not have cardiogenic shock but received primary reperfusion on the criteria of severe hypoxaemia and severe RV dysfunction.

Systemic thrombolysis was associated with a reduction of the Brescia-COVID Respiratory Severity Scale (BCRSS)^{8,9} in five patients, recording a reduction from 3 to 1 in 2/5 patients, and from 3 to 2 in 3/5 patients. The BCRSS is a stepwise management approach to COVID-19 patients based on bedside patient clinical severity. This scale was adopted and used to define objectively the patient's response to treatment.

In addition, 60% (3/5) of the patients with available data had an initial improvement in their PaO₂/FiO₂ ratio ranging from a 19% improvement (Patient 3) to a 156% improvement (Patient 6). It was also associated with a decrease of the RV dysfunction and the RV/LV ratio at 24 h after thrombolysis.

No major bleeding events occurred after the thrombolysis. The overall mortality rate after systemic thrombolysis was 43% (3/7). Although no autopsies were performed, the main hypothesis is a death due to ARDS, and cytokine release syndrome.

(Patient 7 had improvement in echography criteria before dying and patient 5 had clinical improvement before the refractory cardiac arrest.)

Antiphospholipid antibodies were found in 2/5 patients (40%). However, the patients had no history of spontaneous venous thromboembolic events, and these antibodies can also arise transiently in patients with critical illness and various infections.¹⁰

Moreover, in our study, COVID-19 patients have a marked elevation in measured C-reactive protein [average C-reactive protein (CRP) level of 86 mg/mL] and many assays to detect lupus anticoagulants are sensitive to the presence of CRP, resulting in false positive results.¹¹

In COVID-19 patients suffering from ARDS, the gas exchange is already limited and additional PE-related intrapulmonary shunting, alter the remaining exchange capacity. Thus, systemic thrombolysis may restore a part of the respiratory exchange capacity.

Moreover, a case series of three patients¹² in whom fibrinolytic therapy was used led to a reduced mortality and marked improvements in oxygenation. In phase 1 clinical trial on pigs with induced ARDS, Hardaway et al.¹³ had shown a reduced mortality and marked improvements in oxygenation.

Two ongoing trials are investigating the efficacy of rtPA in COVID-19 related ARDS without PE based on the hypothesis of pulmonary microvascular thrombosis underlying ARDS.^{14,15}

More studies are needed to determine the benefit of the systemic thrombolysis for PE in patients with COVID-19, especially in the case of non-high-risk PE.

In our series, PE occurred after hospitalization in ICU and despite classic preventive anticoagulation in two patients. It was associated with the presence of a DVT in 66% (4/6 patients). Although of unproven benefit, it may suggest the need to increase the intensity of

thromboprophylaxis in the COVID-19 patients considering the microvascular thrombosis hypothesis.

Due to a lack of recommendation in PE anticoagulation of COVID-19 patients, our hospital decided to treat them with oral anticoagulation by Rivaroxaban according to standard protocol (15 mg twice a day for 21 days then 20 mg once a day for at least 6 months).

Given the frequency of presentation of acute PE in COVID-19 patients, but also the risks associated with the injection of iodinated contrast medium, the place of CTPA in the evaluation of COVID-19 remains limited.¹⁶

A standardized diagnosis protocol incorporating CTPA for COVID-19 patients with respiratory distress would appear to be advisable, but more studies are needed to determine which COVID-19 patients require CTPA as a complement to the non-contrast CT scan.

Conclusion

The difficulty to identify and accurately manage PE in patients admitted with COVID-19 ARDS, could worsen the short-term prognosis of these patients.

Considering the possible entanglement of pulmonary microvascular thrombosis in COVID-19 related ARDS and despite the poor knowledge of its pathophysiology, our findings suggest that in COVID-19 patients suffering from ARDS who develop PE with RV failure without cardiogenic shock, systemic thrombolysis may be considered.

Larger studies are needed to explain the increased incidence of venous thromboembolic events in patients with COVID-19, to determine the appropriate prophylactic anticoagulation regimen and the benefit for rtPA therapy on respiratory and echographic criteria in patients with COVID-19.

This study was reviewed and approved by the Ethical Committee of Strasbourg (CE-2020-124).

Lead author biography



John Philippe is the Medical doctor diploma in 2019, working as a junior doctor in a cardiology unit in Colmar, France. DIU of intensive care, heart failure, hypertension.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients or patients' next-of-kin in line with COPE guidance.

Conflict of interest: none declared.

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