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RESEARCH ARTICLE

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# Pulmonary perfusion in long-term survivors of COVID-19-related severe acute respiratory distress syndrome treated by extracorporeal membrane oxygenation

**Lucie Miksová**[1] | **Vladimír Dytrych**[1] | **Václav Ptáčník**[2] | **Martin Balík**[3] | **Aleš Linhart**[1] | **Jan Bělohlávek**[1] | **Pavel Jansa**[1]

[1]Clinical Department of Cardiology and Angiology of the 2nd Department of Medicine, General University Hospital in Prague, Prague, Czech Republic

[2]Institute of Nuclear Medicine of the 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic

[3]Department of Anesthesiology and Intensive Care of the 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic

**Correspondence**
Lucie Miksová, Clinical Department of Cardiology and Angiology of the 2nd Department of Medicine, General University Hospital in Prague, U Nemocnice 499/2, Prague 128 08, Czech Republic.
Email: lucie.miksova@vfn.cz

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## Abstract

COVID-19 associates with a hypercoagulant state and an increased risk for venous thromboembolic events (VTEs). Whether severe COVID-19 infection requiring extracorporeal membrane oxygenation (ECMO) support might lead to chronic pulmonary perfusion abnormalities and chronic thromboembolic pulmonary disease/hypertension remains unclear. The purpose of this study was to evaluate chronic pulmonary perfusion abnormalities in long-term survivors of COVID-19-related severe acute respiratory distress syndrome (ARDS) treated by ECMO at our institution. Pulmonary perfusion was examined by ventilation/perfusion (V/Q) single-photon emission computed tomography or V/Q planar scintigraphy at least 3 months after ECMO explantation, comorbidities and incidence of thromboembolic events were recorded as well. Of 172 COVID-19 patients treated by ECMO for severe COVID-19 pneumonia between March 2020 and November 2021, only 80 were successfully weaned from ECMO. Of those, 37 patients were enrolled into the present analysis (27% female, mean age 52 years). Median duration of ECMO support was 12 days. In 24 (65%) patients VTE was recorded in the acute phase (23 patients developed ECMO cannula-related deep vein thrombosis, 5 of them had also a pulmonary embolism, and one thrombus was associated with a central catheter). The median duration between ECMO explantation and assessment of pulmonary perfusion was 420 days. No segmental or larger mismatched perfusion defects were then detected in any patient. In conclusion, in long-term survivors of COVID-19-related ARDS treated by ECMO, no persistent pulmonary perfusion abnormalities were detected although VTE was common.

**KEYWORDS**
chronic thromboembolic pulmonary hypertension, COVID-19 infection, extracorporeal membrane oxygenation, pulmonary perfusion, venous thromboembolic events

## INTRODUCTION

Since late 2019, the global population has been facing a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has rapidly escalated into a worldwide pandemic.[1] The clinical spectrum of this disease ranges from asymptomatic to severe cases characterized by acute respiratory distress syndrome (ARDS), ultimately culminating in respiratory and hemodynamic collapse necessitating extracorporeal membrane oxygenation (ECMO) support. Acute respiratory failure stands as the leading cause of mortality among patients infected with SARS-CoV-2. However, the long-term cardiopulmonary sequelae of COVID-19 infection remain uncertain.

COVID-19 infection is considered to confer a hypercoagulant state elevating the risk of venous thromboembolic events (VTE), such as pulmonary embolism (PE) or deep vein thrombosis (DVT), while arterial thrombosis occurs less frequently.[2] Specific COVID-19 associated coagulopathy and prothrombogenic state triggered by thrombotic microangiopathy, endothelial dysfunction, and activation of the immune-inflammatory cascade, is more likely to affect pulmonary vascular bed than the systemic circulation and is considered to be the main reason of frequent VTE in the acute phase of the infection.[3,4] Pathological studies have already described frequent damage to pulmonary vascular bed in patients who died of COVID-19, including the pulmonary microcirculation.[5] Additionally, Suzuki et al. have documented the thickening of pulmonary vessel walls in COVID-19 fatalities, in contrast to normal pulmonary vessel walls in deceased SARS-CoV-1, MERS, or H1N1 influenza patients. These findings support the hypothesis of chronic changes in pulmonary vascular bed among long-term survivors of COVID-19.[6]

The lung parenchyma is also affected in the acute phase of the infection, mainly as diffuse alveolar damage, which is considered to be a precursor for developing pulmonary fibrosis in certain individuals.[7,8]

Whether these pathological changes in the pulmonary vascular bed can lead to clinically significant chronic pulmonary perfusion abnormalities and eventually to chronic thromboembolic pulmonary disease (CTEPD)/hypertension (CTEPH) is still uncertain. CTEPD/CTEPH is an uncommon and underdiagnosed chronic complication of acute PE.[9,10] According to what we know about CTEPD/CTEPH, the pathophysiology of chronic pulmonary perfusion abnormalities is multifactorial.[11]

Our study aimed to evaluate chronic pulmonary perfusion abnormalities in long-term survivors of severe ARDS caused by COVID-19 infection treated by ECMO. The incidence of VTE in the acute phase of COVID-19 was also assessed.

## METHODS

We performed a single-center trial evaluating chronic pulmonary perfusion abnormalities by V/Q SPECT (ventilation/perfusion single-photon emission computed tomography) or V/Q planar scintigraphy (ventilation/perfusion) in long-term survivors of severe COVID-19 ARDS treated by ECMO between March 2020 and November 2021. V/Q planar scintigraphy was used in one patient due to his excessive weight preventing using of the V/Q SPECT machine. All enrolled patients received therapeutic doses of unfractionated heparin as anticoagulation therapy during ECMO and most of them had initially venovenous (VV) ECMO (35 patients, 94.6%). The rest two patients had venoarterial (VA) ECMO at the beginning. Patients were included at least 3 months after ECMO explantation.

Demographic data, risk factors associated with the severity of SARS-CoV-2 infection, duration of ECMO support, the initial indication of ECMO, the occurrence of thromboembolic complication attributed to either the infection itself or ECMO, and prevalence of acute PE during the acute phase were assessed.

Patients enrolled in the trial were scheduled for a single check-up visit at our hospital, during which they underwent V/Q SPECT or V/Q planar scintigraphy and clinical assessment. These imaging findings were evaluated by an experienced nuclear medicine specialist. The positive V/Q SPECT was defined as one or more segmental or more proximal mismatched perfusion defects.

The study was approved by the local Ethics committee (Ethics Committee in General University Hospital in Prague, No. 115/22 S-IV). All patients gave written informed consent agreeing to data collection and analysis for scientific purposes.

Continuous variables were described by valid number (n), mean (standard deviation) and median (5th and 95th percentile). Absolute and relative frequencies were used for a description of categorical variables.

## RESULTS

Between March 2020 and November 2021, a total of 172 patients were admitted into the ICU of General University Hospital in Prague with severe COVID-19 ARDS and were treated by ECMO. Among them, 92 patients (53.5%) died while on ECMO. ECMO was successfully explanted in 80 patients (46.5%). Out of the 80 patients who had

ECMO explanted, 43 (53.8% of all survivors) were excluded from our research due to their refusal to participate in the follow-up or their unavailability to be contacted via phone calls (Figure 1). Consequently, a total of 37 patients (mean age 52.4 ± 9.3 years, 27% female) were enrolled into the study. When comparing enrolled and unenrolled patients, we found similar mean age (52.4 ± 9.3 vs. 49,6 ± 10.0), slightly higher proportion of female patients (27% vs. 36%), similar mean BMI (33 ± 7.0 vs. 30 ± 5.9 kg/m$^2$) and similar median duration of ECMO treatment (12 [9, 14] vs. 15 days [10, 21]). Additionally, PE during the acute phase of COVID-19 occurred in 13.5% of enrolled patients versus 18.2% of unenrolled patients. Baseline demographics and prevalence of risk factors associated with severe COVID-19 infection in our selected population are presented in Table 1. No patient had a history of previous VTE.

The median duration of ECMO treatment was 12 days [9, 14]. The 35 patients (94.6%) had initially VV ECMO and two patients (5,4%) had VA ECMO for concomitant acute right ventricular failure related to severe ARDS. However, both patients were eventually switched to VV ECMO. At the time of ECMO initiation, 36 patients were intubated and only one had noninvasive ventilation support. All patients in our cohort were anticoagulated in the acute phase, regarding to ECMO support.

In total, 24 patients (64,9% of all patients) developed VTE (DVT/PE) during the acute phase of COVID-19 infection. Among these patients, only one patient had DVT diagnosed before implantation of ECMO (thrombosis of vena cava inferior). The remaining 23 patients (62.2% of all patients) developed ECMO cannula-related DVT. Within this group of 23 patients with ECMO cannula-related DVT, seven patients had also VTE in other locations. Specifically, one had central venous catheter-associated DVT, one had thrombus in the right ventricle and five patients (13.5% of all patients) had acute PE diagnosed by CT pulmonary angiography. Two cases of PE were diagnosed before implantation of ECMO, two during ECMO support and one after ECMO explanation. There were no lower extremity DVT not related to ECMO cannulas. VTE during the acute phase of COVID-19 infection are presented in Table 2.

All V/Q SPECTs and V/Q planar scintigraphy, at a median of 420 days [331, 456] after ECMO explantation, were negative according to the definition above. Patients with prolonged time between ECMO explantation and assessment of pulmonary perfusion (above the median of 420 days), were older (mean age in patients above the median 55.7 ± 5.9 vs. 48.8 ± 10.6 y.o.), were more female (33 vs. 22%) and had shorter duration of ECMO

**TABLE 1** Demography of enrolled patients and prevalence of risk factors of severe COVID-19 infection.

| | | *n* | % |
|---|---|---|---|
| Gender | Female | 10 | 27.0 |
| | Male | 27 | 73.0 |
| Age (mean) | 52.4 ± 9.3 y.o. | | |
| BMI (mean) | 33 ± 6.7 kg/m$^2$ | | |
| Risk factors for severe COVID-19 | Arterial hypertension | 17 | 45.9 |
| | Bronchial asthma | 4 | 10.8 |
| | Malignancy | 3 | 8.1 |
| | Obstructive sleep apnea | 2 | 5.4 |
| | Diabetes mellitus | 2 | 5.4 |
| | Hormonal therapy | 2 | 5.4 |
| | CAD | 1 | 2.7 |
| | Chronic kidney disease | 1 | 2.7 |
| | COPD | 0 | 0 |

Abbreviations: BMI, body mass index, CAD, coronary artery disease, COPD, chronic obstructive pulmonary disease.

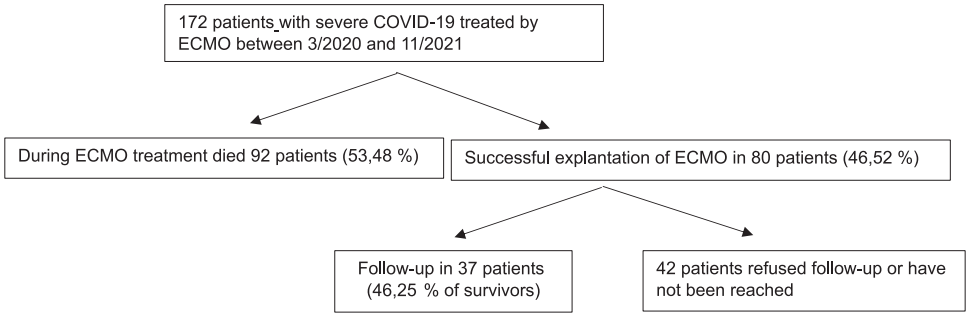


**FIGURE 1** Overview of all patients with severe COVID-19 requiring extracorporeal membrane oxygenation (ECMO) support in General University Hospital in Prague and their follow-up with involvement in our research.

**TABLE 2** Venous thromboembolic events in the acute phase of COVID-19 infection.

| | *N* | % (from 37 patients) |
|---|---|---|
| VTE (in total) | 24 | 64.9 |
| ECMO Cannula-associated DVT | 23 | 62.2 |
| Cannula-associated DVT + VTE in another localization | 7 | 18.9 |
| -Pulmonary embolism | 5 | 13.5 |
| -Central venous catheter-associated DVT | 1 | 2.7 |
| -Thrombus in the right ventricle | 1 | 2.7 |

Abbreviations: DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; VTE, venous thromboembolic event.

(median 11 [7, 13] vs. 15 [9.5; 25.3] days). BMI and number of patients with matched as well as mismatched V/Q defects were similar in both groups - below and above the median. Clinically insignificant findings of subsegmental mismatched defects in lung perfusion and ventilation were diagnosed in two patients, the first one had one defect, and the other one had two defects. Given the high negative predictive value of V/Q SPECT for the diagnosis of CTEPD/CTEPH and the negative findings in all V/Q SPECTs, we did not recommend further diagnostic workups for CTEPD/CTEPH, such as echocardiography, computed tomography (CT)/invasive pulmonary angiography, or right heart catheterization. Seven patients (18.9%) had matching ventilation/perfusion defects on V/Q SPECT.

In our cohort of patients, analyzed for suspected pulmonary perfusion abnormalities, there was a female patient with matching V/Q defects, severe restrictive lung involvement, signs of severe pulmonary hypertension on echocardiography, confirmed by right heart catheterization, we considered specific vasodilatation therapy due to severe pulmonary hypertension group 3 or group 1 with lung phenotype. The potential link between COVID-19 infection and pulmonary arterial hypertension is under discussion.[7]

## DISCUSSION

Despite the high prothrombogenic and procoagulant state of COVID-19 infection itself, we did not prove an increased incidence of significant pulmonary perfusion abnormalities in long-term survivors of severe COVID-19 ARDS treated by ECMO.

Patients treated by ECMO are in general at increased risk of thromboembolic events mainly caused by a biomaterial-induced inflammatory response of ECMO and the underlying illness itself, despite the anticoagulation therapy.[12,13] The risk of thrombosis is even higher in ECMO support indicated for cardiopulmonary complications of acute COVID-19 infection. The prevalence of VTE in patients on ECMO is correlated with the ECMO duration, which was longer in COVID-19 patients than in non-COVID-19 patients on VV ECMO for ARDS.[14,15] Furthermore, there is strong evidence that COVID-19 infection itself creates a prothrombogenic and procoagulant state so not only patients requiring ECMO but all patients with severe COVID-19 infection are at increased risk of VTE (20%–30% in published literature.[16,17] Of 24 patients with VTE, only one had been diagnosed with thrombosis of VCI before ECMO initiation and did not develop ECMO cannula-related DVT. The development of VTE in this case might be triggered by elevated blood levels of factor VIII known from the patient's history, in combination with a procoagulant state caused by COVID-19 infection itself. In this case, there is no association between thrombosis and the presence of artificial materials in the bloodstream (catheters, ECMO cannulas, and so on).

The incidence of CTEPD/CTEPH in our research may have been prevented by full anticoagulation therapy in the acute phase of the infection because of the ECMO treatment. On the other hand, despite the anticoagulation therapy, VTE during the acute phase were still frequent in our cohort of patients.

The prevalence of PE in the acute phase of COVID-19 with severe ARDS treated by ECMO in our research was 13.51%. This is in correlation with published data, that indicate a range of prevalence from 0% to 37%.[13,15,18–22] PE in the acute phase may have been underdiagnosed in our study due to the limited use of computed tomography pulmonary angiography (CTPA), which was performed only in seven patients based on clinical indication. Moreover, it is known that COVID-19-associated PE tends to be located in more peripheral vessels,[23] which can lead to missed diagnoses on conventional CT scans. DECT (dual-energy CT) has shown more precise results in detecting peripheral PE than conventional CT scans.[24] The prevalence of PE in patients with VV ECMO for non-COVID-19 ARDS is lower, ranging from 2% to 10%.[15,25,26] In patients with severe COVID-19 pneumonia with no need for ECMO support, it ranges from 13% to 23%.[16,17,27,28]

The V/Q SPECT and V/Q planar scintigraphy, used in our study, are recommended in current pulmonary hypertension guidelines in the diagnostic workup of CTEPD/CTEPH.[9] It is known that ventilation-perfusion scanning is a very sensitive method in the diagnosis of chronic pulmonary perfusion abnormalities at the

segmental pulmonary arterial level, but slightly worse in specificity in comparison to CTPA.[29] V/Q SPECT and DECT allow visualization of peripheral pulmonary vessel lesions, while CTPA is limited to segmental and less subsegmental pulmonary arteries. DECT seems to be a promising, so far noninferior to V/Q SPECT, method in the diagnosis of CTEPD/CTEPH, hence more research needs to be done.[30] While talking about acute PE, V/Q SPECT and CTPA are equal for diagnosis, on the other hand, V/Q planar scintigraphy is inferior to these methods.[31]

One of the limitations of our study is a small group of analyzed patients and significant patient loss to follow-up. This loss can be caused by the death of the patients or refusal to participate in the research. On the other hand, the demographic and clinical characteristics during the acute phase of the infection were similar between the enrolled and unenrolled patient groups. This similarity makes it possible to assume a similar development of pulmonary reperfusion even in unenrolled patients. The negative result of our research can be also biased by the long follow-up. Patients who could potentially suffer from significant pulmonary perfusion abnormalities may have already died, on the other hand, those without perfusion abnormalities survived and participated in our research. Another limitation is an incomplete assessment of PE in the acute phase of the infection according to the fact, that only symptomatic patients underwent CTPA, which could lead us to a lower total incidence of VTE in the acute phase. Moreover, we could underdiagnose peripheral PE in patients examined by CTPA as mentioned above.

In conclusion, we did not find chronic lung perfusion abnormalities typical for CTEPD/CTEPH in long-term survivors of severe COVID-19 ARDS treated by ECMO despite the high risk of thrombotic and thromboembolic events during the acute phase of the infection in patients treated by ECMO. On the other hand, we did identify a patient with severe precapillary pulmonary hypertension, which is not classified as a CTEPH, as a possible long-term sequela of COVID-19 infection. It is important to note that there is limited research on the long-term cardio-pulmonary consequences of COVID-19, including pulmonary hypertension, and more long-term investigations are warranted to better understand these outcomes.

## AUTHOR CONTRIBUTIONS

**Lucie Miksová**: Conceptualization; methodology; validation; formal analysis; investigation, resources, visualization; project administration, writing—original draft preparation; visualization. **Vladimír Dytrych**: Conceptualization; methodology; validation; formal analysis; investigation, resources; project administration; writing—original draft preparation. **Václav Ptáčník**: Investigation, resources; writing—review and editing. **Martin Balík**: Resources; supervisor; writing—review and editing. **Aleš Linhart**: Resources; supervisor; writing—review and editing. **Jan Bělohlávek**: Methodology; validation; resources; supervisor; writing—review and editing; writing—review and editing. **Pavel Jansa**: Conceptualization; methodology; validation; formal analysis; investigation; resources; visualization; supervisor; project administration; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

Bělohlávek Jan is European ELSO Steering Committee member. The remaining authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

The study was approved by the Prague General University Hospital's research ethics committee.

## ORCID

*Lucie Miksová* http://orcid.org/0009-0007-5043-2281
*Martin Balík* http://orcid.org/0000-0003-1864-2143

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