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Clinical observations of COVID-19 infection in patients with chronic thromboembolic pulmonary hypertension

Aim	To present clinical observations of the novel coronavirus infection (COVID-19) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) after a surgical intervention in the form of thromobendarterectomy from pulmonary artery branches.
Material and methods	The Acad. E.N. Meshalkin National Medical Research Center performed 127 open surgical interventions for CTEPH in the form of thromobendarterectomy from 2016 through 2020. The present study enrolled 113 patients included into the follow-up care group and into the Center Registry who were followed up for more than 6 months after the surgery. Clinical and functional features of COVID-19 were evaluated in the studied group.
Results	In the follow-up care group, 5 (4.4%) postoperative CTEPH patients had COVID-19. One patient had asymptomatic disease, and others had typical clinical symptoms and bilateral polysegmental pneumonia. There were no cases requiring artificial ventilation and no lethal outcomes. All patients with COVID-19 received anticoagulants as a basis therapy for CTEPH, and two patients who had residual pulmonary arterial hypertension (PAH) additionally received a PAH-specific therapy. During the treatment of COVID-19, no adjustment of the anticoagulant or PAH-specific therapy was required.
Conclusion	The group of patients with CTEPH is a unique pathophysiological model for studying the effect of COVID-19 under the conditions of compromised pulmonary circulation. In the studied follow-up care group, the COVID-19 morbidity was 4.4% without fatal outcomes. Evaluation of the role of chronic anticoagulant and PAH-specific therapy in COVID-19 postoperative patients as well as evaluation of the role of COVID-19 in CTEPH progression merit further investigation.

Keywords	Chronic thromboembolic pulmonary hypertension; novel coronavirus infection; COVID-19
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Introduction

The novel coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) remains a significant concern of the health systems, affecting millions of people worldwide [1, 2]. This disease poses the greatest danger for the elderly and patients with chronic cardiovascular and respiratory diseases [3, 4].

SARS-Cov-2 is known to cause severe endothelial dysfunction through mechanisms resembling pulmonary hypertension, such as inflammation, hypoxia, and microthrombosis [5]. The possibility of residual endothelial damage leading to the development of chronic pulmonary vascular remodeling in COVID-19 survivors requires special care and follow-up, due to the risk of chronic thromboembolic pulmonary hypertension (CTEPH) [3].

In this context, patients with CTEPH of a non-infectious origin present a unique clinical model for studying the effects of SARS-Cov-2 on the pulmonary vascular bed. The pathophysiological processes occurring during CTEPH affect both the cardiovascular and respiratory systems, and lead to characteristic manifestations, such as dyspnea and exercise intolerance [6]. The remodeling of large and small pulmonary vessels, impaired pulmonary perfusion, pulmonary congestion, and hemostatic disorders in CTEPH are contributory factors to an increased risk of infectious respiratory diseases [3]. Thus, a characteristic feature of this model is the mutual negative influence of the mechanisms

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of endothelial damage, formation of microthrombi, and fibrotic changes to the pulmonary tissue. These are common to CTEPH and COVID-19, on the one hand, while on the other hand there is a possible protective effect of continuous anticoagulant and pulmonary arterial hypertension (PAH) specific therapy in patients with CTEPH on the COVID-19 manifestations.

Only a few cases of COVID-19 in patients with CTEPH have been reported in the literature [7, 8]. This can be explained by the low prevalence of CTEPH in the general population and a better awareness among follow-up patients about the need to take appropriate COVID-19 precautions. However, the vulnerability of the respiratory system to infectious diseases in CTEPH necessitates further study and systematization of COVID-19 cases in these patients.

Objective

To provide clinical observations for COVID-19 in patients with CTEPH who have undergone pulmonary thrombendarterectomy (PTE).

Material and methods

Between 2016 and 2020, 127 open PTE surgeries were performed to treat CTEPH in the E. N. Meshalkin National Medical Research Center. At the time of surgical intervention, the mean age was 51±6.4 years. There were 76 (60%) male and 51 (40%) female patients. Eleven (8.7%) deaths were reported during hospital stay after PTE. Three patients died from non-infectious causes in the long-term follow period. This retrospective single-center study included 113 patients included in the register and who received follow-up in the Center. The follow-up period was more than 6 months after surgery. The study was carried out following the Good Clinical Practice and the Declaration of Helsinki. All patients signed the informed consent to participate in the study. The ethics committee of the Center approved the study protocol.

Preoperative verification of the CTEPH diagnosis, estimation of the pulmonary vascular damage, and pulmonary perfusion were based on the results of right heart catheterization and pulmonary angiography. All patients underwent PTE under deep hypothermia (18°C) and circulatory arrest.

COVID-19 was diagnosed and its severity estimated by the results of clinical and laboratory examinations, chest X-ray and/or multislice computed tomography (MSCT). Source medical records were collected by means of remote communication methods.

Table 1. Baseline characteristics of patients with chronic thromboembolic pulmonary hypertension before surgery

Parameter	Total group, n = 113
Male, n (%)	68 (60)
Age, years	51±7.1
Body mass index, kg/m^2	28±6.3
NYHA functional class II, n (%) III, n (%) IV, n (%)	 15 (13) 88 (78) 10 (9)
Genetically confirmed thrombophilia, n (%)	54 (48)
Lower limb thrombophlebitis, n (%)	83 (73)
Coronary artery disease, n (%)	14 (12)
Chronic obstructive pulmonary disease, n (%)	35 (31)
Diabetes mellitus, n (%)	2 (1.8)
Left ventricular ejection fraction, %	66±6.9
Right ventricular fractional area change, %	39±4.1
Mean pulmonary artery pressure, mm Hg	46±9.5
Pulmonary vascular resistance, dyn*s*cm^5	770±122
Arterial oxygenation,%	94±2.0
PAH-specific therapy before surgery, n (%)	42 (37)

PAH, pulmonary arterial hypertension.

Sex, age, anthropometric data, clinical and functional state of the respiratory and cardiovascular systems, the presence of post-PTE complications, the presence of comorbidities, compliance with drug therapy were also analyzed in the study.

The data obtained was analyzed using the Statistica 6.1 software suite. The normality of distribution of the parameters of interest was verified using the Shapiro – Wilk W-test. Quantitative variables are presented as the mean values, and standard deviations (M±SD). Qualitative variables are expressed as the absolute values and/or percentages.

Results

The baseline characteristics of patients with CTEPH and history of PTE included in the study are set out in Table 1. PAH-specific therapy was administered to 42 (37%) patients with CTEPH before surgical treatment. PAH-specific therapy

was used in 17 (15%) patients in the long-term follow-up period after PTE, in order to treat residual pulmonary hypertension. Anticoagulant treatment was indicated in all patients who underwent PTE. Warfarin was administered in 39% of patients (daily dose 2.5–2.75 mg with INR control), rivaroxaban (daily dose 20 mg), or dabigatran etexilate (daily dose 300 mg) in 52.2% of patients. In the long-term follow-up period, 10 (8.8%) did not comply with these recommendations or took drugs irregularly. There were no patients lost to follow-up after PTE.

Of all the patients with CTEPH included in the follow-up group after PTE, there were 5 (4.4%) cases of COVID-19 from March 2020 to September 2020 (Table 2).

One patient had asymptomatic COVID-19, and the test for COVID-19 was carried out for the purposes of traveling abroad. The remaining 4 cases developed with clinical manifestations and were complicated by bilateral polysegmental pneumonia. These patients did not travel from their region of residence, and the three of them had contact with COVID-19 patients.

The typical clinical picture of COVID-19 in patients with CTEPH who underwent PTE was manifested in a fever lasting 3 days or more, asthenia, and dyspnea. All patients underwent chest MSCT,

Table 2. Characteristics of patients who underwent surgical treatment of chronic thromboembolic pulmonary hypertension and had confirmed COVID-19

Patient	S	Sh	D	M	Z
Sex	Female	Female	Male	Male	Male
Age, years	52	63	40	69	37
Time after surgery	4 years	2 years	4 years	12 months	3 years
Anticoagulant therapy, daily dose	Warfarin 2.5 mg	Warfarin 2.5 mg	Rivaroxaban 20 mg	Warfarin 2.75 mg	Warfarin 2.5 mg
PAH-specific therapy, daily dose	Not needed	Not needed	Not needed	Riociguat 3 mg	Riociguat 3 mg
Onset of the disease	June 2020	August 2020	July 2020	June 2020	July 2020
Time in hospital, days	14	34	20	22	–
Time in ICU, days	0	3	0	0	–
Clinical symptoms of COVID-19	Fever for 3 days, dyspnea, dry cough, asthenia, increased BP to 150/100 mm Hg	Fever for more than 20 days, sore throat, dyspnea, asthenia, tachycardia, decreased BP	Fever for 7 days, dyspnea, chest pain, cough, loss of smell and taste, tachycardia, decreased BP, episodes of loss of consciousness	Fever for 4 days, sore throat, dyspnea, asthenia, increased BP to 160/100 mm Hg	Asymptomatic course
Chest MSCT	Signs of bilateral polysegmental pneumonia with 60% of pulmonary tissue involved	Viral bilateral polysegmental pneumonia with more than 50% of pulmonary tissue involved	Signs of bilateral polysegmental pneumonia more than 50% of pulmonary tissue involved	Signs bilateral polysegmental pneumonia, ground glass opacities, more than 25% of pulmonary tissue involved	Not applicable
Oxygen blood saturation,%	84%	80%	96%	90%	97%
COVID-19 treatment, daily dose	Oseltamivir 150 mg, azithromycin 500 mg, warfarin 2.5 mg, bromhexine 16 mg, vitamin C 1000 mg	Oseltamivir 150 mg, levofloxacin 500 mg, amoxicillin + clavulanic acid 1500 mg, warfarin 2.5 mg, ambroxol 90 mg, vitamin C 1000 mg	Oseltamivir 150 mg, azithromycin 500 mg, rivaroxaban 20 mg, bromhexine 16 mg, vitamin C 1000 mg	Oseltamivir 150 mg, levofloxacin 500 mg, warfarin 2.75 mg, bromhexine 16 mg, vitamin C 1000 mg	Not applicable

BP, blood pressure; PAH, pulmonary arterial hypertension; MSCT, multislice computed tomography; ICU, intensive care unit.

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which verified bilateral polysegmental pneumonia with the 25–60% involvement of pulmonary tissue.

The treatment of symptomatic COVID-19 was initiated on the first day of the disease. All four patients were admitted to the hospital on days 3–7 after the onset of clinical symptoms due to progressing dyspnea (respiratory rate more than 25 breaths per minute), oxygen blood saturation reduced to 80–90% and/or low blood pressure. In one case, low blood pressure was accompanied by episodes of unconsciousness.

All patients received antiviral drugs, anticoagulants, mucolytics, and antipyretics. Due to the high risk of concurrent infection, empirical antibiotic therapy was used. In one case of severe pneumonia, a 63-year-old female patient was transferred to the intensive care unit. She received oxygen inhalation, and was placed in the prone position with a positive response. Decreasing blood pressure in two patients and increasing blood pressure in another two patients required dose adjustments of antihypertensive drugs.

Oropharyngeal swabs for SARS-CoV-2 were tested in all patients. Patients were discharged from hospital after two negative test results and the relief of infectious symptoms on days 14–34 of hospital stay. There were no fatalities.

Patients with CTEPH who underwent PTE and had confirmed COVID-19 contacted the physician in charge of the follow-up group over the phone. Remote monitoring and face-to-face examinations were performed by physicians from the infectious disease department during the hospital stay, and by general practitioners in the local outpatient clinics and/or ambulance physicians. Patients with CTEPH who underwent PTE during the pandemic were recommended to self-isolate, maintain personal hygiene and wear masks in public. Echocardiography performed at the hospital revealed neither significant myocardial wall motion disorders, nor was there a significant increase in the pulmonary artery pressure compared with the findings before COVID-19-related pneumonia. Episodes of thromboembolism were reported during treatment and after COVID-19.

It should be noted that all patients with COVID-19 followed the recommendations for anticoagulant therapy as the background treatment. Four patients took warfarin, and one patient took rivaroxaban. Two patients received PAH-specific therapy due to residual pulmonary hypertension after PTE. Anticoagulant and PAH-specific treatment did not require correction during the treatment of COVID-19.

Discussion

Patients with chronic pulmonary hypertension, including those of thromboembolic origin, are at risk of respiratory infectious diseases [1, 2]. We analyzed cases of COVID-19 in patients with CTEPH who underwent surgery and were included in the follow-up register of the National Medical Research Center.

There is no data from large international trials on the incidence of COVID-19 in patients with CTEPH. According to our data, 5 patients had laboratory-confirmed COVID-19 from among the 113 patients followed up after PTE. The data obtained is consistent with a number of studies which show that the prevalence of COVID-19 in patients with CTEPH is similar to that in the general population [7, 8].

Pneumonia with severe pulmonary tissue involvement in the form of diffuse alveolar damage is the most common complication of COVID-19. About 3–4% of patients have acute respiratory distress syndrome [1, 2]. Postinfectious damage of pulmonary tissue, pulmonary fibrosis, and pulmonary microvascular injury in patients with a history of COVID-19 raise essential medical and social problems, i.e., decreased physical performance and work capacity in the general population.

The clinical picture COVID-19 did not have any distinguishing features in the study group. Except for an asymptomatic carrier of SARS-CoV-2, all patients had fever, dyspnea, and asthenia. MSCT showed signs of bilateral polysegmental pneumonia with 25–60% pulmonary tissue involvement. Contrary to the opinion of experts with respect to the high risk of severe COVID-19 in patients with chronic cardiovascular diseases [9], long-term respiratory support was not required. There were no fatalities in the study group.

There were no episodes of thromboembolism, progression of pulmonary hypertension during COVID-19 in patients with CTEPH who underwent PTE. The difference between the methods of COVID-19 treatment in patients with CTEPH who underwent PTE is in the absence of the need for additional anticoagulant therapy. This is due to the continuous use of this category of drugs in patients of the study group.

Some authors have hypothesized the existence of pathophysiological similarities in pulmonary vascular lesions in CTEPH and COVID-19 [10].

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Lung damage associated with COVID-19 is the result of inter-related pathophysiological processes, in which endothelial dysfunction plays an important role, and can lead to the development of thrombosis and vasomotor disturbances. Endothelial lesion and pulmonary microvascular thrombosis lead to ventilation-perfusion mismatch and vascular tone dysregulation, which aggravates hypoxemia [11, 12].

Thus, the pathomorphology of COVID-19 goes beyond the inflammatory response to viral infection. The endothelial lesion in COVID-19, which can lead to coagulopathy, inflammation, and vasoconstriction, is key to the pathogenesis of severe lung injury [3]. Some studies show more pronounced damage to the pulmonary vascular bed in COVID-19, when compared to other respiratory infections, including H1N1 influenza [11].

The role of continuous anticoagulation and PAH-specific therapies in patients with CTEPH during the COVID-19 pandemic also requires further research [3, 12]. It is interesting to note that most of the patients studied (4/5) take warfarin as an anticoagulant therapy, whereas only 39% of patients took warfarin in the general follow-up group. Residual pulmonary hypertension, requiring the administration of PAH-specific treatment in the study group, was reported in 17 (15%) patients with CTEPH who underwent PTE. Among the COVID-19 cases, two of the five patients had residual pulmonary hypertension and received PAH-specific therapy.

This study was limited by the retrospective design. Some patients could have had mild or asymptomatic COVID-19, since laboratory tests were not performed due to the absence of indications. Due to a limited number of observations, the data obtained needs to be interpreted carefully and then studied.

Conclusion

The group of patients with CTEPH is a unique model for studying the effects of COVID-19 in the compromised pulmonary vascular bed. The incidence of COVID-19 in the follow-up group was 4.4%, and no deaths were reported. The role of continuous anticoagulant and PAH-specific therapies during COVID-19 in patients with CTEPH who underwent surgery and the assessment of the role of COVID-19 in the progression of CTEPH merit further study.

No conflict of interest is reported.

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REFERENCES

1. World Health Organisation. Coronavirus Disease (COVID-19). Situation Report – 189. Av. at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200727-covid-19-sitrep-189.pdf?sfvrsn=b93a6913_2.
2. Ministry of Health of Russian Federation. Temporary methodical recommendations. Prevention, diagnosis and treatment of new coronavirus infection (COVID-2019). Version 8.1 (01.10.2020). Av. at: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/052/219/original/Временные_MP_COVID-19_(v.8.1).pdf?1601561462. 2020. [Russian: Министерство здравоохранения РФ. Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)». Версия 8.1 (01.10.2020). Доступно на: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/052/219/original/Временные_MP_COVID-19_(v.8.1).pdf?1601561462]
3. Nuche J, Segura de la Cal T, Jiménez López Guarch C, López-Medrano F, Delgado CP-O, Ynsaurriaga FA et al. Effect of Coronavirus Disease 2019 in Pulmonary Circulation. The Particular Scenario of Precapillary Pulmonary Hypertension. Diagnostics. 2020;10(8):548. DOI: 10.3390/diagnostics10080548
4. Avdeev S.N., Tsareva N.N., Merzhoeva Z.M., Trushenko N.V., Yaroshetskiy A.I. Practical guidance for oxygen treatment and respiratory support of patients with COVID-19 infection before admission to intensive care unit. Pulmonology. 2020;30(2):151–63. [Russian: Авдеев С.Н., Царева Н.А., Мержоева З.М., Трушенко Н.В., Ярошецкий А.И. Практические рекомендации по кислородотерапии и респираторной поддержке пациентов с COVID-19 на дореанимационном этапе. Пульмонология. 2020;30(2):151-63]. DOI: 10.18093/0869-0189-2020-30-2-151-163
5. Potus F, Mai V, Lebret M, Malenfant S, Breton-Gagnon E, Lajoie AC et al. Novel insights on the pulmonary vascular consequences of COVID-19. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2020;319(2):L277–88. DOI: 10.1152/ajplung.00195.2020
6. Exercise and Sports Pulmonology: Pathophysiological Adaptations and Rehabilitation. Cogo A, Bonini M, Onorati P, editors – Cham: Springer International Publishing;2019. – 216 p. ISBN 978-3-030-05257-7
7. Horn EM, Chakinala M, Oudiz R, Joseloff E, Rosenzweig EB. Could pulmonary arterial hypertension patients be at a lower risk from severe COVID-19? Pulmonary Circulation. 2020;10(2):204589402092279. DOI: 10.1177/2045894020922799
8. Segura de la Cal T, Nuche J, Jiménez López-Guarch C, Pérez-Olivares C, Velázquez M, López-Medrano F et al. Unexpected Favourable Course of Coronavirus Disease 2019 in Chronic Thromboembolic Pulmonary Hypertension Patients. Archivos de Bronconeumología. 2020;56(11):749–52. DOI: 10.1016/j.arbres.2020.06.004
9. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020;5(7):811–8. DOI: 10.1001/jamacardio.2020.1017
10. Magrone T, Magrone M, Jirillo E. Focus on Receptors for Coronaviruses with Special Reference to Angiotensin- Converting Enzyme 2 as a Potential Drug Target - A Perspective.

Endocrine, Metabolic & Immune Disorders - Drug Targets. 2020;20(6):807–11. DOI: 10.2174/1871530320666200427112902

11. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. New England Journal of Medicine. 2020;383(2):120–8. DOI: 10.1056/NEJMoa2015432
12. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. Journal of Thrombosis and Thrombolysis. 2020;50(1):54–67. DOI: 10.1007/s11239-020-02134-3

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