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Review

How to deal with chronic thromboembolic pulmonary arterial hypertension (CTEPH) during the COVID-19 pandemic: Too many gray zones to be considered

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ABSTRACT

In December 2019, a serious number of patients with pneumonia was first announced in Wuhan and, since March 11, 2020, the World Health Organization (WHO) has declared coronavirus disease 2019 (COVID-2019) caused by SARS-CoV-2 to be a pandemic and a very severe global health problem. Severity about this disease is associated with an increasing age and comorbidities such as chronic heart and lung disease. Chronic thromboembolic pulmonary hypertension (CTEPH), another important and fatal disease, is a specific type of pulmonary hypertension characterized by obstruction or occlusion of subsegmental, segmental, or larger pulmonary arteries by the post-embolic fibrotic material which has a definitive cure by pulmonary endarterectomy performed under cardiopulmonary bypass and total circulatory arrest. In this article, we examined thoroughly and enlightened some of the gray zones in CTEPH patients for healthcare providers with the aim of providing a reasonable algorithm in the era of COVID-19 pandemic.

Keywords: COVID-19, pandemic, pulmonary heart disease.

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2; COVID-19) pandemic has changed not only the paradigm of maintenance of healthcare system for healthcare providers and governments, but also the whole world since December 2019, and there is a growing number of data accumulating from may centers across the globe.[1,2] It has been established that age and underlying cardiovascular diseases such as hypertension, diabetes, and myocardial infarction are the most important risk factors for mortality from COVID-19 pneumonia.[3,4] Malnutrition and superimposed bacterial infections may also worsen the prognosis and prolong the length of intensive care unit (ICU) stay. In some cases, multiple organ dysfunction may develop and the most common organ damage is lung, followed by the heart, kidney, and liver. During this outbreak, several reports have been published, mainly focusing on minimizing contamination and protecting the healthcare providers. However, data are still scarce about the management of patients with diseases other than COVID-19 infection urging us to obtain expert opinions. In that regard, patients with chronic thromboembolic pulmonary hypertension (CTEPH) constitute one of the most challenging patient populations. During this outbreak, many reports have been published, mainly concentrated on protecting the patients and healthcare providers. However, data are still lacking about management of CTEPH patients. Common challenges faced by healthcare professionals during the pandemic

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include prioritization of resources (ventilators, ICU facilities and intensive care professionals) to patients with COVID-19 infections, risk for viral transmission between patients and staff, contamination of the equipment which are all limiting the state-of-the-art management approaches to CTEPH patients. The scope of this document is to summarize the possible challenges and how these challenges may be addressed during the pandemic with an emphasis on the rational use of diagnostic imaging techniques, adaptation of safe pharmacological treatment, approach to patient selection for pulmonary endarterectomy (PEA), and full disinfection for safeguarding the patient, healthcare providers, and ICU facilities.

While reading this document, one should consider that the presented viewpoint may be subjected to modification due to insufficient evidence-based scientific data and the rapidly changing global situation. This document also seeks an answer to the following questions:

a. Are all CTEPH patients at high risk for COVID-19?
b. What are the suggestions for the diagnosis in new patients?
c. What are the suggestions for surgical treatment of CTEPH?
d. What are the suggestions for medical treatment of CTEPH patients?
e. What are the suggestions for the follow-up of CTEPH patients?

COVID- 19 AND CTEPH

COVID-19 has caused about 100,000 deaths in nearly 1.600,000 patients worldwide and it has been reported that patients with an underlying pulmonary and cardiovascular disease (CVD) are at an increased risk for adverse outcomes from COVID-19.[5] Chronic thromboembolic pulmonary hypertension is a specific type of pulmonary hypertension (PH)[6,7] characterized by an obstruction or occlusion of subsegmental, segmental, or larger pulmonary arteries by post-embolic fibrotic material, causing the elevation of pulmonary arterial hypertension (PAH) and right heart failure.[8] These features make CTEPH patients vulnerable and fragile in the time of outbreak.

In general, CTEPH is categorized as Group 4 in the classification of PH (Table 1).[6-8] The diagnosis is based on the following criteria:

1. Pulmonary hypertension confirmed by right heart catheterization (RHC) (mean pulmonary arterial pressure ≥25 mmHg and pulmonary arterial wedge pressure ≤15 mmHg at rest)
2. Mismatch on ventilation/perfusion (V/Q) scintigraphy (usually V/Q single-photon emission computed tomography [SPECT]) with at least one large perfusion defect in one segment or in two subsegments, or evidence of pulmonary vascular lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) or pulmonary angiography
3. These findings should be obtained after at least three months of effective anticoagulation.[8]

Table 1. Classification of pulmonary hypertension

1. PAH
- Idiopathic PAH
- Heritable PAH
  - BMPR2
  - Other mutations
- Drug- and toxin-induced
- Associated with
  - CTD
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis

1′ PVOD and/or PCH
1″ Persistent PH of the newborn

2. PH due to left hear disease
- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valcular disease
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia

COPD

Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental lung diseases

4. CTEPH and other pulmonary artery obstructions

5. PH with unclear multifactorial mechanisms
- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

PAH: Pulmonary arterial hypertension; BMPR2: Bone morphogenetic protein receptor type 2; CTD: Connective tissue disease; HIV: Human immunodeficiency virus; PVOD: Pulmonary veno-occlusive disease; PCH: Pulmonary capillary haemangiomatosis; PH: Pulmonary hypertension; COPD: Chronic obstructive pulmonary disease; CTEPH: Chronic thromboembolic pulmonary hypertension.

As a general rule, operability should be assessed in all cases with CTEPH, as PEA is the most effective treatment of CTEPH, except for severe comorbid situations. The work-up of patients requires an extensive use of imaging techniques and cardiac catheterization. This situation, however, raises many concerns during the COVID-19 pandemic: *(i)* performance of PEA will increase the need for extracorporeal membrane oxygenation (ECMO) and ventilators, besides the risk for dissemination of COVID-19 and exposure of the healthcare professionals and the equipment during hospitalization; *(ii)* COVID-19 infection will aggravate the symptoms of patients with CTEPH due to already restricted pulmonary capacity, leading to hemodynamic deterioration and complicate the clinical course of the disease; and *(iii)* additional thromboembolic events may be triggered due to viral infection and predisposition to hypercoagulation during the inflammatory state, hospital stay, and due to the lack of mobilization.

CHALLENGES IN DIAGNOSIS

The traditional approach to diagnosis of CTEPH includes a multidisciplinary teamwork. Echocardiography, CT pulmonary angiography (CTPA), and ventilation-perfusion (V/Q) scan are the first line diagnostic options. There is a sufficient number of evidences of PH on echocardiography associated with evidence of mismatched segmental perfusion defects on the V/Q scan for referring the patient to a center with expertise in treating patients with PH. In the era of COVID-19 pandemic, due to travelling restrictions, it is key to treat the patient locally and refer only if the referral is life-saving in the short-term. Communications with PAH centers should be strengthened for local patient management.

Patients with dyspnea and hypoxia should be considered as having suspected COVID-19 pneumonia and any diagnostic test should be undertaken with appropriate protective measures against contamination.[5,9] Since there is a high risk for myocardial involvement due to COVID-19 infection, transthoracic echocardiography (TTE) is the first step imaging tool to make the diagnosis and it is very important to rigorously assess pre-test probability with the use of scoring systems for pulmonary thromboembolism and limit imaging to appropriate patients to minimize the risk for further dissemination of the disease and consumption of protective equipment. The recommendations of the European Association of Cardiovascular Imaging on precautions, indications, prioritization, and protection for patients and healthcare personnel during cardiac imaging in the era of COVID-19 pandemic should be strictly followed.[10] A focused cardiac ultrasound protocol is highly recommended to limit the time of exposure with the patient in the echocardiography lab.[10] For suspected PH, the echocardiographic examination should be curtailed to the assessment of right and left ventricular functions and morphology, inferior vena cava, gross evaluation of the valves other than Doppler recordings of tricuspid regurgitation and flow through the right ventricular outflow.

In the acute setting, any raise in troponins or B-type natriuretic peptide (BNP) levels should be considered with reservation before searching for pulmonary embolism or CTEPH. A high proportion of patients with COVID-19 infection experience elevated troponins and BNP levels without obstructive coronary lesions or without pulmonary embolism due to myocarditis or myocardial infarction with normal coronary arteries (i.e., myocardial infarction with non-obstructive coronary arteries [MINOCA]). Care should be taken to assess left ventricular function first in such cases. On the other hand, D-dimer elevations and disseminated coagulopathy may be common in patients with severe forms of COVID-19, as in other severe infections disease, such as systemic human immunodeficiency virus.[11]

The chest radiograph is the most commonly used imaging test in COVID-19 patients, followed by CT to confirm the diagnosis of COVID-19 pneumonia. The CTPA may give the opportunity to confirm pulmonary embolism with one single examination. However, interpretation of the CT scan may be difficult in the random association of CTEPH and COVID-19 findings, particularly in a new patient with a history of pulmonary embolism lasting for more than three months (with effective anticoagulation for at least three months).

Although ventilation perfusion (V/Q) scan is the integral imaging tool to rule out CTEPH in the traditional algorithm,[10] during the pandemic, it is crucial to assess the presence of lung parenchymal opacities on a chest radiograph or CT scan first including CTPA. If the lungs are clear and CTEPH or pulmonary embolism suspicion persists, it is plausible to proceed with lung perfusion scintigraphy without a ventilation component. If the perfusion scan does not demonstrate segmental defects, the scan is deemed negative for embolism. A complete V/Q scan should be undertaken, only if there are

contraindications for CTPA, after serological tests are performed for COVID-19 and if the patient is severely symptomatic. Aerosol precautions are mandatory for COVID-19-positive patients. Any follow-up imaging exam including TTE in stable patients with CTEPH should be re-scheduled. The six-minute walking distance tests can be also postponed during the outbreak.

CHALLENGES IN RHC

The RHC is mandatory to confirm the diagnosis of any PAH before any PAH specific treatment. Pre- and postoperative pulmonary vascular resistance are long-term predictors of prognosis for CTEPH patients.[5] The RHC may be crucial in severely symptomatic patients with CTEPH, particularly to discriminate the relative contribution of left-sided heart failure due to COVID-19 infection. In preference, RHC should be undertaken after COVID-19 serological tests are obtained. In COVID-19-positive patients, if they are severely symptomatic under optimal medical treatment of heart failure and anticoagulation, RHC can be undertaken with aerosol precautions, only if the short-term outcome is likely to be impacted. Otherwise, the procedure should be re-scheduled to minimize the dissemination of the virus during patient transport and the contamination of the catheterization lab. In addition, negative-pressure catheterization labs dedicated to COVID-19 infection are not available in many centers. Troponins and pro-BNP levels are not helpful in these circumstances. However, increased N-terminal-proBNP and BNP are often used as predictors of right heart failure. Symptomatic patients with elevated proBNP levels may undergo echocardiographic evaluation and dual CT angiography, followed by a RHC which may help the diagnosis for CTEPH patients.

CHALLENGES FOR PEA IN COVID-19 PANDEMIC AND INFLAMMATORY RESPONSES

Pulmonary endarterectomy is the treatment of choice for CTEPH in the absence of life-threatening comorbidities and this type of open heart surgery necessitates a true bilateral endarterectomy through the medial layer of the pulmonary arteries. The level of disease is defined by the proximal extension of the cast and the classification is made according to the material removed surgically. Level I defines a disease in the right or left main pulmonary artery; Level IC a unilateral disease; Level II a disease in the lobar branches; Level III a disease in the proximal segmental arteries; and Level IV a disease in the distal segmental and subsegmental pulmonary branches (Table 1). Cardiopulmonary bypass is followed by circulatory arrest in deep hypothermia which are necessary to keep the surgical field free of blood via the bronchopulmonary collaterals and also to protect the brain functions.[12]

Development of novel therapies and effective prevention are an urgent need, particularly for life-threatening severe acute respiratory distress syndrome and hyper-inflammatory syndrome which is characterized by a fulminant and fatal hypercytokinemia with multi-organ failure. Several cytokines are involved in the disease pathogenesis.[2]

Whether a patient with CTEPH can be successfully treated by PEA is determined by multiple factors which cannot be easily standardized. Principally, these include the technical operability and the risk-benefit ratio for PEA (i.e., accessibility of the obstructions, preoperative hemodynamics, and comorbidities), the expertise of the surgical team, and available resources. During this pandemic, the multidisciplinary team must keep in mind that there will be some shortages of ventilators. Another important issue is the use of ECMO. The use of intra- and postoperative ECMO therapy is part of the standard care at CTEPH centers, particularly for severe cases with elevated pulmonary vascular resistance index greater than 12 Wood units.[5,13] Acute respiratory distress due to early postoperative reperfusion edema may be bridged with veno-venous ECMO. In contrast, veno-arterial ECMO support is indicated for right ventricular pump failure in persistent severe PH.[13]

Although there is neither consensus nor enough evidence for the use of ECMO in COVID-19 patients, it should be always considered as a powerful weapon in our arsenal like inhale nitric oxide. Postponing the PEA candidates who have elevated pulmonary vascular resistance may be a good idea in case of having a famine in the number of ECMOs and medical staff.

Major surgery and anesthesia usually produce inflammatory and immune responses in human beings. In addition, extracorporeal circulation has been presented to be the cause of the main immune response during cardiac surgery. The continuous exposure of blood to the non-endothelial surfaces (perfusion circuit), cold cardiac ischemia, and hypothermia produce a systemic inflammatory response (i.e., activation

of coagulation pathways, complement system, and production of tissue factors and several cytokines). The inflammatory reaction can intensify systemic inflammatory response syndrome. The inflammatory response during cardiac surgery occurs due to not only cardiopulmonary bypass, but also surgical trauma, anesthesia, cardioplegia and myocardial ischemia, cardiac manipulation, heparin, and protamine. All these can be fatal events which complicate the postoperative period in COVID-19 patients. Therefore, all elective patients should be postponed, if possible, and these patients should receive medical treatment until this outbreak is over. If a patient needs an urgent surgery (this important decision should be given by a multidisciplinary team), all strategies should be done to minimize inflammation including heparin-coated circuits, perioperative corticosteroids, intraoperative ultrafiltration, and meticulous postoperative care.[14-16]

CHALLENGES IN MEDICAL TREATMENT

Supportive medical treatment for CTEPH consists of anticoagulants and diuretics, and long-term oxygen therapy in cases of hypoxemia.[14,17] Lifelong anticoagulation is recommended even after PEA.[5] Currently, only riociguat, an oral soluble guanylate cyclase stimulator, has been approved for the treatment of inoperable or persistent/recurrent CTEPH after PEA.[18] However, it poses two challenges: the uptitration visits of riociguat may be difficult at the beginning of the treatment and drug interactions.

Currently, hydroxychloroquine, remdesivir, and azithromycin are the most often used therapies in COVID-19 patients and methylprednisolon may be occasionally needed in severe pulmonary infections.[19] No drug-drug interaction has been reported so far with riociguat (Figure 1).[20,21] However, riociguat may increase the exposure of atazanavir and lopinavir. Switching from warfarin to low-molecular-weight heparin (LMWH) should be undertaken in ICU patients. Although there is not enough data about new oral anticoagulants (NOACs) in the treatment of CTEPH, warfarin may be considered to be switched to a NOAC or LMWH in ambulatory patients with poor control of their international normalized ratio (INR) to decrease the number of visits, if there are no contraindications to the use of NOACs (i.e., antiphospholipid antibodies, creatinine clearance less than 15 mL/min).

Where warfarin remains the only choice, in stable patients, INR tests can be performed every 12 weeks, or self-monitorization with remote communication whenever necessary is a favorable option to minimize attendances for INR monitoring in ambulatory patients, regardless of COVID-19 infection. Co-administration of warfarin with antiviral agents may have a potential interaction and, therefore, careful monitorization is needed, unless switch from warfarin to a NOAC is possible.

Drugs	Hydroxychloroquine	Azithromycin	Lopinavir/Ritonavir	Favipiravir	Remdesivir	Oseltamivir	Ribavirine
Anti-coagulant							
Heparin							
Enoxaparin							
Apixaban							
Rivaroxaban							
Edoxaban							
Dabigatran							
Warfarin							
Anti-hypertensives Pulmonary hypertension							
Iloprost							
Riociguat							
Epoprostenol							

No interaction
Low risk
High risk
Do not use together

Figure 1. Drug-drug interactions of experimental COVID-19 treatments.

One may also consider prophylactic LMWH in patients who are hospitalized for COVID-19 infection and have a low risk profile for bleeding.

REMOTE COMMUNICATION WITH PATIENTS

As we are living in a digital age, it is of utmost importance for CTEPH patients and families to reach professionals, when necessary. Therefore, teleconferences, webinars, forums, and telephone visits will be helpful in not only for answering their questions, but also supporting patients/families emotionally.

In conclusion, since the COVID-19 pandemic has emerged as an unexpected healthcare crisis across the world, routine healthcare delivery has been compromised by critical resource constraints in many fields such as diagnostic testing, hospital beds, ventilators, and ICU facilities. In this vulnerable patient group, all patients should be discussed by the CTEPH Team including a pulmonologist, cardiologist, cardiovascular surgeon, radiologist, intensivist, and anesthesiologist to make the accurate and rapid diagnosis and tailor the management strategy. Patients should receive their medical treatment without any interruption and, thus, they should reach their doctors or nurses via telemedicine or any other media of digital and social media age. Any surgical intervention should be considered, only if it is likely to substantially change the patient outcome. Elective interventions should be re-scheduled, while patients are receiving optimal medical treatments. Protecting both patients and healthcare providers has a vital importance for all of us.

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