Pulmonary Hypertension and COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a primary respiratory infectious disease, which can result in pulmonary and cardiovascular complications. From its first appearance in the city of Wuhan (China), the infection spread worldwide, leading to its declaration as a pandemic on March 11, 2020. Clinical research on SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) suggests that the virus may determine changes in the pulmonary hemodynamics through mechanisms of endothelial dysfunction, vascular leak, thrombotic microangiopathy, and venous thromboembolism that are similar to those leading to pulmonary hypertension (PH). Current available studies report echocardiographic signs of PH in approximately 12 to 13% of hospitalized patients with COVID-19. Those with chronic pulmonary obstructive disease, congestive heart failure, pulmonary embolism, and prior PH are at increased risk to develop or worsen PH. Evidence of PH seems to be associated with increased disease severity and poor outcome. Because of the importance of the pulmonary hemodynamics in the pathophysiology of COVID-19, there is growing interest in exploring the potential therapeutical benefits of inhaled vasodilators in patients with COVID-19. Treatment with inhaled nitric oxide and prostacyclin has shown encouraging results through improvement of systemic oxygenation, reduction of systolic pulmonary arterial pressure, and prevention of right ventricular failure; however, data from randomized control trials are still required.

Keywords
► COVID-19
► pulmonary hypertension
► right heart failure

Zusammenfassung

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense single-stranded RNA virus belonging to the family Coronaviridae. From its first appearance in the city of Wuhan (China), the infection spread worldwide, leading to its declaration as a pandemic on March 11, 2020. Clinical manifestations of COVID-19 vary from mild respiratory symptoms to severe and critical pulmonary disease and patients with underlying pulmonary and cardiovascular disease are at increased risk for adverse outcomes. COVID-19 may result in pulmonary and cardiovascular complications, including acute respiratory distress syndrome (ARDS), venous thromboembolism, and acute cardiac injury.

Clinical research on SARS-CoV-2 suggests that the virus may determine changes in the pulmonary hemodynamics through mechanisms of endothelial dysfunction, vascular leak, and thrombotic microangiopathy that are similar to those leading to pulmonary vascular disease. However, a causative role of COVID-19 in inducing pulmonary hypertension (PH) has to date not been demonstrated and the prognostic role of PH in COVID-19 is still on study. The present article aims to review pathophysiological mechanisms, clinical characteristics, and therapeutical aspects relating COVID-19 and PH.

Definition and Pathophysiology of Pulmonary Hypertension

The term PH refers to the presence of high pulmonary vascular pressure, which can be the result of different underlying disorders. By definition, PH is an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as assessed by right heart catheterization. Precapillary PH is characterized by an mPAP ≥ 25 mmHg, a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and a pulmonary vascular resistance (PVR) > 3 WU. Postcapillary PH is defined by mPAP ≥ 25 mmHg and PCWP > 15 mmHg. In combined post- and precapillary PH, PCWP is > 15 mmHg, diastolic pressure gradient (diastolic PAP – mean PCWP) ≥ 7 mmHg and/or PVR > 3 WU. Currently clinical classification of PH categorizes patients with PH in five distinct groups according to pathophysiology and possible treatment strategies (Table 1).

The pathophysiology of PH is multifactorial and characterized by an imbalance in vasoconstriction and vasodilation, thrombosis, cell proliferation, and remodeling of the wall of the pulmonary arteries leading to an increase of PVR. Pulmonary vasoconstriction is an early component of the PH process and is partly related to endothelial dysfunction, which is characterized by an imbalance between impaired production of vasodilators such as nitric oxide and prostacyclin (PGI2) and overexpression of vasoconstrictors, for example endothelin-1 (ET-1).

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<th>Table 1 Classification of pulmonary hypertension</th>
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<td><strong>Etiology</strong></td>
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<td>Pulmonary arterial hypertension</td>
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<td>PH due to lung diseases</td>
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<td>Chronic thromboembolic PH</td>
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<td>PH with unclear and/or multifactorial mechanisms</td>
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Abbreviations: DPG, diastolic pressure gradient (diastolic PAP – mean PCWP); mPAP, mean pulmonary arterial pressure; PCWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.
Autoimmunity and inflammation mediated by cytokines and chemokines also contribute to pulmonary vascular alterations. These alterations induce an increase of PVR and promote vascular remodeling, and therefore represent important pharmacological targets.⁷

PH in Patients with COVID-19

Epidemiology
PH is a common condition in patients with COVID-19. Currently available observational studies report echocardiographic signs of PH in approximately 12 to 13% of hospitalized patients with COVID-19.⁸,⁹ A small study with right heart catheterization found a prevalence of PH of nearly 80% in ventilated patients with severe COVID-19.¹⁰

The current clinical research does not distinguish between PH of new onset in the context of acute viral infection and pre-existent and/or worsened PH. Considering the high prevalence of chronic lung and heart disease among patients with COVID-19, it can be expected that many patients already had signs of PH before. Data on patients with pulmonary arterial hypertension (PAH) experiencing COVID-19 are to date very limited.¹¹,¹²

Pathophysiology
SARS-CoV-2 infection may alter pulmonary hemodynamics through different mechanisms, partially overlapping the general pathophysiology of PH. These include: (1) endothelitis and vasculitis; (2) thrombotic microangiopathy; (3) venous thromboembolism; and (4) hemodynamic alterations consequent to ARDS and mechanical ventilation (► Fig. 1).⁴,¹³–¹⁵ A small autopsy study found a recurrent distinctive morphological pattern in lung samplings infected by SARS-CoV-2, including: (1) severe endothelial injury associated with intracellular SARS-CoV-2 virus; (2) widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries; and (3) significant new vessel growth through a mechanism of intussusceptive angiogenesis.¹³ Furthermore, intense platelet activation has been reported in several studies.¹⁶–¹⁸ In particular, Zaid and colleagues¹⁶ described that platelets express proinflammatory molecules, contain viral RNA, and are hyperactivated, contributing to the cytokine storm and thrombosis. Thrombotic sequelae of SARS-CoV-2 infection may affect both macro- and microcirculation and pulmonary embolism (PE) is a recurrent complication that may result in acute PH and right ventricular (RV) failure.¹⁹–²⁴ Hemodynamic alterations consequent to ARDS may finally contribute to the development of PH in severe COVID-19. Classically ARDS is characterized by acute respiratory failure with noncardiogenic pulmonary edema and consequent impaired gas exchange, decreased lung compliance, and PH.²⁵ ARDS may present with an atypical form in COVID-19, characterized by significant dissociation between the relatively well-preserved lung mechanics and compliance, and the severity of hypoxemia associated with large intrapulmonary shunts.²⁶,²⁷ Consistently with this observation, patients often display little dyspnea despite profound

Fig. 1 Pathogenesis of pulmonary hypertension in COVID-19.
hypoxemia ("happy hypoxemia"), as reported by Guan and colleagues. This is supposed to result from the failure of the homeostatic oxygen-sensing systems, including the mechanism of hypoxic vasoconstriction (HPV) and the carotid body function. HPV physiologically diverts blood flow from poorly ventilated alveoli, therefore optimizing ventilation-perfusion (VQ) matching; on the contrary its loss causes intrapulmonary shunts with consequent hypoxemia. The hypothesis of the loss of HPV seems to be supported by data from a small study reporting atypical low values of PVR measured through right heart catheterization in ventilated patients with COVID-19-associated ARDS.

As already underlined, many patients experiencing COVID-19 are affected by chronic cardiopulmonary disease, including chronic obstructive pulmonary disease (COPD) and congestive heart failure, which are proven risk factors for SARS-CoV-2 infection in terms of prevalence and adverse outcome. In these patients, pre-existent PH may be worsened by the acute viral infection through the pathophysiological mechanisms cited above.

**Diagnostics**

Distinct diagnostics of PH would require a comprehensive setting of investigations including right heart catheterization. However, in the current COVID-19 pandemic, which requires care delivery to an increased number of patients in emergency setting, transthoracic echocardiographic assessment is used for diagnosis of PH in most studies. Echocardiography allows Doppler measurement of peak tricuspid regurgitation velocity (TRV). Together with estimation of right atrial pressure based on measurement of inferior vena cava diameter and simplified Bernoulli equation, estimation of systolic pulmonary arterial pressure (sPAP) in mmHg can be performed. Other echocardiographic signs suggesting PH include: (1) right ventricle/left ventricle basal diameter ratio >1.0; (2) flatter of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole); (3) RV outflow Doppler acceleration time <105 milliseconds and/or mid-systolic notching; (4) early diastolic pulmonary regurgitation velocity >2.2 m/s; (5) inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration); and (6) right atrial area (end-systole) >18 cm². A TRV >2.9 milliseconds together with other echocardiographic signs cited above suggests a high probability of PH. Although not such accurate as right heart catheterization, echocardiography allows sufficient identification of patients with severe PH. However, this method may be less sensitive in patients with mild PH. Computed tomography (CT) allows sensitive diagnostics of pulmonal impairment in COVID-19. Typical findings are ground-glass opacifications with eventual consolidation. Chest CT is not performed in all hospitalized patients with COVID-19 and is usually reserved for severe cases. Patients with echocardiographic signs of PH may be good candidates for further CT scan, as it allows the diagnosis of concomitant PE and can identify high-risk patients with profound radiographic pulmonary impairment.

Right heart catheterization may be performed to measure pulmonary pressure directly and to monitor volume status, vascular resistance, and cardiac output in severe cases on mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO). Although pulmonary artery catheter allows precise monitoring, no clinical benefit of routine use was found in the past for critically ill patients with ARDS. An observational study run on 21 patients with COVID-19-associated ARDS examined with right heart catheterization reported that PH was mostly postcapillary, underlining complex pathogenesis of COVID-19 and association with the cardiovascular system.

**Clinical and Prognostic Significance**

PH is investigated in many studies concerning COVID-19. For this review of current evidence, we performed a comprehensive systematic search on major electronic databases including PubMed, Google scholar, Medline, and Scopus to find articles published between December 1, 2019 and March 1, 2021. In addition, public databases such as the World Health Organization Centers for Disease Control were used. The following keywords were adopted: “coronavirus disease 2019,” “COVID-19,” “pulmonary arterial hypertension,” and “pulmonary hypertension.” In our search we analyzed prospective and retrospective observational studies, as well as case publications in English in scientific journals and references cited in those articles (Table 2).

The presence of PH seems to be associated with increased disease severity and poor outcome in COVID-19, in terms of requirement of mechanical ventilation, admission to intensive care unit, and mortality. In particular, Deng and colleagues reported that PH was more frequent in patients with severe COVID-19 compared with those experiencing mild to moderate course. Moreover, evidence of PH was statistically significant in predicting an adverse outcome (primary composite endpoint including admission to intensive care unit, requirement of mechanical ventilation or ECMO, and mortality). Similarly, it was found that an increase of sPAP detected by echocardiography was associated with disease severity in terms of radiological lung involvement, laboratory findings, oxygenation status, and need of noninvasive ventilation.

PH can result in RV overload and thus acute RV failure, which may further complicate the clinical course of the viral infection. RV longitudinal strain (RVLS) assessed with speckle-tracking echocardiography was able to predict higher mortality risk in patients with COVID-19 in a retrospective study by Li and colleagues. Patients with lower RVLS had also enlarged RV chamber, reduced tricuspid annular plane systolic excursion (TAPSE), and increased sPAP compared with those with higher RVLS. These findings were also supported by Rath et al, who reported that impaired RV function and tricuspid regurgitation > grade 1 were significantly associated with higher mortality.

Echocardiographic signs of PH and RV failure may also be related with acute PE, as observed by Scudiero and colleagues. Consistent with previous data reporting a prevalence of PE of 7 to 30%, they described PE in 14% of...
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<td>Deng et al.</td>
<td>Retrospective</td>
<td>122</td>
<td>To investigate myocardial injury in COVID-19 patients. PH was assessed in TTE according to the ESC-guidelines criteria.</td>
<td>• Signs of PH were present in 13% of all patients, in 21% with severe COVID-19, and 2% with mild to moderate disease. Evidence of PH was statistically significant in predicting an adverse outcome (admission to intensive care unit, requirement of mechanical ventilation or extracorporeal membrane oxygenation, and mortality).</td>
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<td>Pagnesi et al.</td>
<td>Prospective</td>
<td>200</td>
<td>To investigate presence and prognostic significance of echocardiographic signs of PH and RVD in COVID-19 patients.</td>
<td>• PH and RVD were present in 12 and 14.5% of all patients respectively, 4% had both PH and RVD. Patients with PH and/or RVD had more frequently a history of prior cardiac comorbidities including congestive heart failure, AF and known cardiomyopathy, and higher biomarkers of cardiac involvement (high-sensitivity troponin-T and NT-proBNP). Patients with PH showed signs of more severe infection in terms of radiological lung involvement, laboratory findings, oxygenation status, and need of NIV compared with patients without PH. PH was associated with higher rates of in-hospital death or ICU admission.</td>
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<tr>
<td>Scudiero et al.</td>
<td>Retrospective</td>
<td>224</td>
<td>To assess prevalence, predictors, and clinical outcome of PE in COVID-19 patients. All patients underwent CT pulmonary angiography and TTE.</td>
<td>• PE was observed in 14% patients. • PE patients had higher D-dimer level and higher prevalence of myocardial injury, cardiogenic shock, and increased mortality rate. • PE patients had lower values of TAPSE and higher sPAP.</td>
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<tr>
<td>Li et al.</td>
<td>Prospective</td>
<td>120</td>
<td>To evaluate the prognostic value of RVLS assessed through speckle-tracking echocardiography in COVID-19 patients.</td>
<td>• RVLS was able to predict higher risk of mortality in patients with COVID-19 independently of other echocardiographic parameters.</td>
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<tr>
<td>Feng et al.</td>
<td>Case series</td>
<td>5</td>
<td>To analyze whether iNO was beneficial in patients with severe COVID-19 requiring mechanical ventilation. Patients with pre-existent heart diseases were excluded.</td>
<td>• Three patients received iNO treatment. Normalization or not worsening of sPAP and increase of PaO₂/FiO₂ were observed in all cases. Two of them survived. • Two patients did not receive iNO. Both cases experienced right heart failure, sudden decrease of sPAP and PaO₂/FiO₂, and finally died.</td>
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<tr>
<td>Sonti et al.</td>
<td>Retrospective study</td>
<td>80</td>
<td>To analyze potential effect of iEpo in the management of hypoxemia in patients mechanically ventilated for COVID-19.</td>
<td>• Clinically significant improvement in PaO₂/FiO₂ (+10% from the baseline value) was observed in 50% of patients.</td>
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hospitalized patients with COVID-19. Patients with PE showed lower values of TAPSE and higher sPAP compared with those without PE. Moreover, the presence of PE was associated with higher prevalence of myocardial injury, cardiogenic shock, and increased mortality rate. Due to the prognostic significance of PH, current studies underline the importance of transthoracic echocardiography in the diagnostic evaluation of patients with COVID-19. Signs of PH may identify low-symptomatic patients who are at increased risk of adverse outcome and thus candidates for close monitoring and aggressive treatment.

**Therapeutic Perspectives**

Based on the discussed importance of pulmonary hemodynamics in the pathophysiology of COVID-19, indirect evidence suggests that current therapies of PAH targeting nitric oxide (NO), prostaglandin, and endothelin pathways may partially influence the outcome of COVID-19 patients, especially in the context of ARDS.

NO is a vasodilative molecule produced from L-arginine in vascular endothelial cells. It diffuses into adjacent vascular smooth muscle and, through activation of the cyclic guanosine monophosphate (cGMP) pathway, induces smooth muscle relaxation, which results in decreased vascular tone in systemic and pulmonary circulation. Additional effects of NO include anti-inflammatory functions as well as suppression of smooth muscle proliferation and platelet aggregation.

Phosphodiesterase 5 (PDE-5) inhibitors are potent unspecific vasodilative drugs targeting the NO pathway. Their mechanism derives from inhibition of PDE-5, which prolongs the action of cGMP avoiding its enzymatic degradation. PDE-5 inhibitors have been traditionally successfully used in the treatment of PAH, while clinical research failed to demonstrate their efficacy in the management of ARDS. The use of PDE-5 inhibitors has been supposed to be beneficial in COVID-19 to counteract the changes in pulmonary hemodynamics and the intense inflammatory response. However, clinical data reporting the use of this class of drugs in COVID-19 are still lacking.

Unlike PDE5 inhibitors, inhaled nitric oxide (iNO) induces selective pulmonary vasodilation in ventilated areas of the lung, resulting in improvement of oxygenation due to better VQ-matching and amelioration of PH. Clinical trials and meta-analysis in ARDS showed that treatment with iNO induces a transitory improvement of oxygenation but has no impact on patients’ outcome and therefore is not routinely recommended. Small studies suggest that treatment with iNO may be beneficial in patients with COVID-19 through improvement of systemic oxygenation and reduction of PAP and thus RV afterload.

PGI2 is produced by endothelial cells and induces vascular smooth muscle relaxation and inhibition of platelet aggregation. Furthermore, it seems to have cytoprotective and antiproliferative properties. Inhaled PGI2 analogs represent a cornerstone of therapy of PAH, while they are not beneficial in the context of ARDS. Their use in patients with severe COVID-19 showed positive results in two clinical studies, reporting modest but statistically significant

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<tr>
<td>Moezini et al.</td>
<td>Case series</td>
<td>8</td>
<td>To explore potential benefit of iloprost in patients with severe COVID-19 and digital ischemia.</td>
<td>After a continuous 5-day infusion, a sustained clinical improvement in the digital ischemia and in cardiovascular and respiratory parameters, decreasing oxygen requirements, increasing PaO2/FiO2, and normalization of HR were observed. The treatment was well tolerated.</td>
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**Table 2** (Continued)

Abbreviations: AF, atrial fibrillation; CT, computed tomography; HR, heart rate; ICU, intensive care unit; iEpo, inhaled epoprostenol; iNO, inhaled nitric oxide; NIV, noninvasive ventilation; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RVD, right ventricular dysfunction; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.
improvement of cardiovascular and respiratory parameters, including systemic oxygenation.\textsuperscript{47,48} Despite some promising results, potential benefits of therapies with iNO and PGI2 analogs must be supported by stronger evidence from randomized trials.

The use of endothelin receptor antagonists (ERAs) may also be of interest in the management of PH in COVID-19. ET-1 is a potent vasoconstrictor, proinflammatory, proliferative, and pro-oxidative glycopeptide, which is overexpressed in PAH.\textsuperscript{49} It has been postulated that in inflammatory stress conditions, such as SARS-CoV-2 infection, high levels of ET-1 may aggravate the lung injury through activation of necroinflammatory pathways and promoting fibroblast differentiation.\textsuperscript{42,50,51} On this basis, the use of ERAs may be beneficial in the management of PH in COVID-19. Clinical data are still lacking.

**Summary**

PH is a common condition associated with COVID-19. Its pathogenesis is complex and includes the following mechanisms: endotheliitis and vasculitis, thrombotic microangiopathy, venous thromboembolism, and ARDS. Many patients with signs of PH suffer from chronic cardiopulmonary diseases such as COPD and congestive heart failure. Current clinical evidence suggests that evidence of PH in patients with COVID-19 may be associated with increased disease severity and poor outcome. This underlines the importance of transthoracic echocardiography in the diagnostic evaluation of patients with COVID-19, to identify those at increased risk of adverse outcome. Because of the importance of the pulmonary hemodynamics in the pathophysiology of COVID-19, indirect evidence suggests that current therapies of PAH targeting the NO, the prostaglandin, and the endothelin pathways may partially influence the outcome of COVID-19 patients, especially in the context of ARDS. Treatments with iNO and inhaled PGI2 have shown encouraging results in small trials through improvement of systemic oxygenation, reduction of sPAP, and prevention of RV failure. However, further investigation in large randomized clinical trials is required.

**Zusammenfassung**


**What Is Known about This Topic?**

- Coronavirus disease 2019 can result in pulmonary and cardiovascular complications.
- Radiological and histological findings suggest that the virus may determine changes in the pulmonary circulation similar to those leading to pulmonary hypertension.

**What Does This Paper Add?**

- This review collects and discusses current available data about the relationship between COVID-19 and pulmonary hypertension.
- Diagnostic and therapeutical options are presented, with particular attention to bed-side echocardiography.
- The detection of pulmonary hypertension may be helpful to identify patients at increased risk of adverse outcome.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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