Management of Patients With Pulmonary Hypertension in COVID-19 Pandemic

Müntecep Aşkar¹, Selvi Aşkar², Medeni Karaduman³, Rabia Çoldur¹

¹Department of Cardiology, Van Yüzüncü Yıl University Medical Faculty, Van, Turkey
²Department of Chest Diseases, Van Yüzüncü Yıl University, Faculty of Medicine, Van, Turkey

ABSTRACT

The new coronavirus (COVID-19) epidemic caused by SARS-CoV-2 has emerged as perhaps the biggest medical problem of our century. Although COVID-19 mainly affects the lungs, it also affects many organs, especially the cardiovascular system. Pulmonary hypertension (PH) is a pulmonary vascular disease described by pulmonary arterial vasoconstriction and remodeling, which may lead to an increased pulmonary artery pressure with varying clinical course and severity depending on the etiology and eventually to right heart failure.

Because of associated comorbidities, patients with PH are likely to face a potential risk of severe complications and mortality and unfortunately, they may have worse outcomes than other patients. The COVID-19 pandemic has brought us new and different challenges in the follow-up and treatment processes of patients with PH. For patients admitting to the hospital, it is important to balance the risk of exposure to COVID-19 with ongoing care and treatment services. However, the COVID-19 outbreak has brought serious challenges to PH centers to weigh the risks and benefits of diagnostic research, including potential exposure to COVID-19, and the timing of initiation of PH-specific treatment in high-risk patients.

In this article, the management of PH patients during the COVID-19 pandemic; problems encountered in diagnosis, clinical follow-up and treatment processes; the different difficulties experienced during hospitalizations have been compiled.

Keywords: COVID-19; Hypertension, Pulmonary; Therapy

Introduction

Coronavirus disease (COVID-19), which first appeared in China, was named severe acute respiratory tract syndrome caused by a new coronavirus. To date, more than 81 million people worldwide and 2.2 million people in our country have been affected by the epidemic. Also, more than 1.8 million (1,2) people in the world and 21 thousand people (2-4) in our country died due to the disease. In people with chronic health problems, especially hypertension, and cardiovascular diseases, the disease is more severe and, unfortunately more fatal. Morbidity and mortality risk is higher in advanced age and male gender.

COVID-19 emerges as one of the biggest threats facing society in this century. Besides its many medical consequences, the epidemic has psychological, social, and economic prices. Therefore, it is essential to understand its pathophysiology and clinical outcomes and to determine appropriate treatment strategies. To date, few reports of pulmonary hypertension (PH) patients with COVID-19 disease have been reported. It is too early to come to this conclusion because the proportion of patients with PH in the population is very low. Usually, living in isolation from the community, close medical follow-up, regular use of preventive medical treatments may explain the low incidence of infection. Pathological characteristics of the endothelial cell structures of PH patients infected with COVID-19, down-regulation of angiotensin-converting enzyme 2 (ACE-2) receptors, which play a fundamental role in both the entry and replication of coronaviruses and also pulmonary arterial hypertension (PAH)-specific drugs used in its treatment may contribute to this (5,6).

Pulmonary Hypertension: PH is a progressive pulmonary vascular disease characterized by pulmonary arterial vasoconstriction remodeling, resulting in increased pulmonary arterial pressure and, consequently, right heart failure.

*Corresponding Author: Müntecep Aşkar, Department of Cardiology, Van Yüzüncü Yıl University Medical Faculty, Dursun Odabaş Medical Center, 65100, Van, Turkey

E-mail: muntecepasker@gmail.com, Tel: +90 (505) 251 47 05, Fax: +90 (432) 212 19 54

ORCID ID: Müntecep Aşkar: 0000-0001-8852-6266, Selvi Aşkar: 0000-0003-4077-8549, Medeni Karaduman: 0000-0002-6080-6335, Rabia Çoldur: 0000-0002-9620-7422

Received: 13.09.2021
### Table 1. Updated Clinical Classification of Pulmonary Hypertension (PH) (9)

<table>
<thead>
<tr>
<th>1. PAH</th>
<th>3. PH due to lung diseases and/or hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1. Idiopathic PAH</td>
<td>3.1. Obstructive lung disease</td>
</tr>
<tr>
<td>1.2. Heritable PAH</td>
<td>3.2. Restrictive lung disease</td>
</tr>
<tr>
<td>1.3. Drug- and toxin-induced PAH</td>
<td>3.3. Other lung disease with mixed restrictive/obstructive pattern</td>
</tr>
<tr>
<td>1.4. PAH associated with:</td>
<td>3.4. Hypoxia without lung disease</td>
</tr>
<tr>
<td>1.4.1. Connective tissue disease</td>
<td>3.5. Developmental lung disorders</td>
</tr>
<tr>
<td>1.4.2. HIV infection</td>
<td>4. PH due to pulmonary artery obstructions</td>
</tr>
<tr>
<td>1.4.3. Portal hypertension</td>
<td>4.1. Chronic thromboembolic PH</td>
</tr>
<tr>
<td>1.4.4. Congenital heart disease</td>
<td>4.2. Other pulmonary artery obstructions</td>
</tr>
<tr>
<td>1.4.5. Schistosomiasis</td>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>1.5. PAH long-term responders to calcium channel blockers</td>
<td>5.1. Haematological disorders</td>
</tr>
<tr>
<td>1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement</td>
<td>5.2. Systemic and metabolic disorders</td>
</tr>
<tr>
<td>1.7. Persistent PH of the newborn syndrome</td>
<td>5.3. Others</td>
</tr>
<tr>
<td>2. PH due to left heart disease</td>
<td>5.4. Complex congenital heart disease</td>
</tr>
<tr>
<td>2.1. PH due to heart failure with preserved LVEF</td>
<td></td>
</tr>
<tr>
<td>2.2. PH due to heart failure with reduced LVEF</td>
<td></td>
</tr>
<tr>
<td>2.3. Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>2.4. Congenital/acquired cardiovascular conditions leading to post-capillary PH</td>
<td></td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction

### Table 2. A Simplified Approach for Risk Stratification in Group 1 PAH (9)

<table>
<thead>
<tr>
<th>Prognostic criteria</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6-min walk distance (6MWD)</td>
<td>&gt; 440 m</td>
<td>165–440 m</td>
<td>&lt; 165 m</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt; 300 ng/mL</td>
<td>300–1400 ng/mL</td>
<td>&gt; 1400 ng/mL</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt; 50 ng/L</td>
<td>50–300 ng/L</td>
<td>&gt; 300 ng/L</td>
</tr>
<tr>
<td>RAP</td>
<td>&lt; 8 mmHg</td>
<td>8–14 mmHg</td>
<td>&gt; 14 mmHg</td>
</tr>
<tr>
<td>CI</td>
<td>≥ 2.5 l/min/m²</td>
<td>2.0–2.4 l/min/m²</td>
<td>&lt; 2.0 l/min/m²</td>
</tr>
<tr>
<td>ScvO₂</td>
<td>≥ 65%</td>
<td>60–65%</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td>Low risk</td>
<td>Intermediate risk</td>
<td>High risk</td>
<td></td>
</tr>
<tr>
<td>At least three low-risk criteria and no high-risk criteria</td>
<td>Definitions of low or high risk not fulfilled</td>
<td>At least two high-risk criteria including CI or ScvO₂</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms of PH are shortness of breath, fatigue, chest pain, palpitations, fainting, and edema, especially with physical activity. In the case of delayed diagnosis and inadequate treatment, PH may cause right ventricular failure, premature death and growing pulmonary vascular resistance.

The first meeting related to PH was held in Geneva in 1973. Here, PH was defined as hemodynamically measured mean pulmonary artery pressure > 25 mmHg at rest in the supine position (7). In the PH guideline published in 2015, the mean resting pulmonary artery pressure (mPAP) as assessed by right heart catheterization was defined as 25 mmHg. Although it is known that normal mPAP at rest is 14 ± 3 mmHg in healthy people, the clinical significance of a mPAP...
value between 21 and 24 mmHg is not clear (8). This confusion was ended at the last PH meeting held in 2018 and PH was defined as mean PAP > 20 mmHg, pulmonary artery wedge pressure (PAWP) < 15mmHg, and pulmonary vascular resistance (PVR) > 3 WU (9). Apart from the hemodynamic definition, some modifications were also made in the disease groups, causing PH (Table 1) (9).

Coronaviruses: Coronaviruses are single-stranded enveloped RNA viruses that are 26 and 32 kb in length belonging to the Coronaviridae family. There are four species in the Orthocoronavirinae subfamily as alpha, beta, gamma, and delta coronavirus. Among them, alpha and beta coronaviruses infect mammals. There are seven subclasses of coronaviruses that humans may acquire: alpha coronaviruses HCoV-NL63 and 229E, which is likely to lead to mild illness in adults; beta coronaviruses Middle East respiratory syndrome (MERS) virus and severe acute respiratory syndrome (SARS) virus; and OC43 and HKU1 which are related to mild disease. COVID-19 is a new beta coronavirus syndrome caused by bats and World Health Organization (WHO) has termed COVID-19 as severe acute respiratory coronavirus 2 (SARS-CoV-2) (10).

Coronavirus receptor binding occurs by spike protein. This protein is encoded by the S gene, which has two subunits, S1 and S2. The receptors of the envelope spike glycoprotein are CD209L for SARS-CoV, SARS-CoV-2, and DPP4 for MERS-CoV and angiotensin-converting enzyme 2 (ACE-2) for SARS-CoV. Membrane fusion occurs at the beginning of SARS-CoV's entry into the cell. After the virus enters the cell, structural proteins are synthesized from viral RNA in the cytoplasm. Following this process, the viral genome begins to multiply, and replication takes place via RNA-dependent RNA polymerase (11).

Pathophysiology: The new coronavirus SARS-CoV-2 exerts its effects in patients with COVID-19 through its interaction with its spike protein and highly expressed ACE-2 receptors in the lung alveolar cells and vascular endothelium (12). Deficiency or down-regulation of ACE-2 disrupts angiotensin II and reduces its impacts on vasoconstriction, fibrosis and endothelial damage (13). This condition causes dysregulation of hypoxic vasoconstrictive mechanisms and increased pulmonary vasoconstriction. However, we should note that a linear relationship between plasma angiotensinogen II levels and viral load in patients with COVID-19 is present and the severity of lung damage (14). Endothelial dysfunction is the starting point for initiating the chain of events causing PH, ventilation/perfusion mismatch, vasoconstriction and hypoxia. A progressive increase in pulmonary artery pressure leads to an increase in ventricle (RV) afterload, which leads to heart failure and also RV dysfunction (Figure 1) (15).

Endothelin-1 is upregulated in PH, and endothelin receptor antagonists targeting the endothelin pathway have been successfully used in the treatment of PH. There is a correlation between

<table>
<thead>
<tr>
<th>Table 3. COVID-19 Drug Interactions (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Ambrisentan</td>
</tr>
<tr>
<td>Bosentan</td>
</tr>
<tr>
<td>Macitentan</td>
</tr>
<tr>
<td>Sildenafil</td>
</tr>
<tr>
<td>Tadalafil</td>
</tr>
<tr>
<td>Riosiguat</td>
</tr>
<tr>
<td>Selexipag</td>
</tr>
<tr>
<td>Epoprostenol</td>
</tr>
<tr>
<td>Iloprost</td>
</tr>
<tr>
<td>Treprostinil</td>
</tr>
</tbody>
</table>
the endothelin system and the renin-angiotensin system (RAS). Endothelin-1 may decrease ACE-2 expression in lung epithelial cells and inhibit vasoconstriction induced by endothelin receptor antagonist, angiotensin II. In addition, it has been shown that angiotensin and endothelin-1 weaken the effects of inflammation and growth on endothelial cells (16,17,18).

In the pathological examination of the lungs in patients with COVID-19, diffuse thrombosis severe disruption of the integrity of the endothelial barrier and damage to endothelial cells were found. Vascular angiogenesis emerges as an important finding in acute respiratory distress syndrome (ARDS) associated with COVID-19 (20). Extensive lung injury results in ARDS followed by interstitial fibrosis. Hypoxia because of ARDS may lead to acute PH and pulmonary vasoconstriction. Inflammatory response and damage to the endothelium may lead to increased coagulation and intravascular thrombosis. Thrombosis, hyperinflammatory response and fibrosis further facilitate the development of PH and subsequent RV dysfunction. Microthrombosis, diffuse microangiopathy and endothelial dysfunction may lead to ventilation-perfusion mismatch. Intrapulmonary right to left shunt and hypoxia may exacerbate further and trigger a vicious cycle that leads to remodeling of the pulmonary vasculature (20,21).

**Follow-up of PH Patients during the COVID-19 Disease:** Patients with clinically stable
pulmonary arterial hypertension (PAH) are evaluated every three to six months, according to the ERS/ESC 2015 guideline. This is due to the vulnerable state of PH patients, their rapid clinical deterioration, and evaluation of treatment efficacy. Due to this fragile condition of PH patients, risk scoring, and risk assessment specific to PH has been formulated (8). At the 6th pulmonary hypertension symposium, PH risk stratification was simplified and updated (9) (Table 2).

Remote interviews are recommended except for the presence of a clinical situation that requires face-to-face interviews and the need for diagnostic testing. Conversations should be made by phone or other means of communication.

While Covid-19 infection can progress with simple respiratory symptoms; it may also progress as severe pneumonia involving all organs, primarily the cardiovascular system.

Severe COVID-19 infection is characterized by rapidly progressing systemic inflammation, proinflammatory cytokine storm, and sepsis, which can lead to life-threatening multi-organ failure (Figure 2). Myocardial infarction, arrhythmias, cardiogenic shock, cardiomyopathy, myocarditis and acute cor pulmonale can be seen in patients with COVID-19 disease. In addition, localized thrombosis in pulmonary vessels is common. Although the incidence of SARS-CoV-2 infection in PH patients is similar to the general population, COVID-19 disease has a worse prognosis in adults with PH. Elderly patients with comorbidities carry a higher risk of mortality due to COVID-19 (23-25).

PH patients with worsening right heart failure, ischemia, sepsis or disease should be evaluated in terms of Covid-19 infection. In the clinical evaluation of patients with PH and established Covid-19 infection, the risk of developing decompensated right heart failure was found to be quite low in cases with mild symptoms (26). These patients may be followed up and treated at home. However, patients with worsening respiratory symptoms should be hospitalized. Patients with severe respiratory symptoms should be followed up in intensive care units of centers that can provide advanced medical services, including extracorporeal life support and lung transplantation. The right ventricle may deteriorate rapidly as a result of hypoxemia and inflammatory cytokine release, so close clinical follow-up is required.

The clinical history of the patient who presents with COVID-19 infection should be questioned and a physical examination should be performed. Comprehensive laboratory tests including blood gas analysis, complete blood count, measurements of D-dimer, brain natriuretic peptide, lactate dehydrogenase, C reactive protein, troponin, procalcitonin and chest X-ray, electrocardiogram, echocardiogram should be performed as soon as possible. If deemed necessary, HRCT imaging records should be obtained with thorax CT.

Initial treatment of hospitalized PH patients with COVID-19 includes treatment of the underlying respiratory viral infection and basic supportive measures. Fluid replacement should be adjusted by evaluating right ventricular preload, vasodilators and inotropic and vasopressor agents should be given according to the clinical condition of the patients (27). PAH-specific medications should not be withdrawn or changed in these patients unless necessary.

Hypoxia and ARDS are very difficult to treat in PH patients with COVID-19 infection. Along with the medical treatment of the cytokine storm that caused it, attention should be paid to the treatment of hypoxia. Continuous oxygen support should be provided to keep the oxygen saturation above 90%. Positive pressure ventilation (BPAP/CPAP) is not preferred because it increases intrathoracic pressure that counteracts RV preload and induces aerosolization. Instead, a high-flow nasal cannula can be used. Intubation should be avoided if possible; severe hypotension and hemodynamic collapse may develop with the contribution of sedative agents used. Therefore, intubation should be done by an experienced specialist, and medical preparation should be made before intubation. Vasopressor drugs should be initiated to protect the patient from sudden collapse due to hypotension before intubation. For general anesthesia, drugs with little impact on cardiac contractility and vascular tone should be preferred. While ventilator settings provide adequate oxygenation and ventilation, keeping the airway pressures at a minimum with low tidal volume and moderate positive end-expiratory pressure should be targeted (28,29).

**PAH Specific Drugs:** The relatively low mortality in PH patients diagnosed with COVID-19 has been attributed to the protective effect of PAH-specific drugs used for other medical conditions. Because of the interaction of drugs commonly used in the treatment of PAH and drugs used for Covid-19, treatment selection, and dose adjustment convey importance (Table 3) (30). COVID-19 disease is characterized by respiratory failure secondary to acute lung injury progressing to ARDS. In addition to direct pathological effects
at the pulmonary system level, it causes coagulopathy in all the systems. Microthrombi associated with hypercoagulopathy have been shown throughout the body, especially in the pulmonary vascular system (31).

**Endothelin receptor antagonists:** Endothelin-1 (ET-1) is a vasoconstrictor polypeptide. In PAH, ET-1 is upregulated, and the imbalance between nitric oxide (NO) and ET-1 causes increased vascular tone and vascular remodeling. Growth factors, cytokines, and other vasoactive constituents induced by Covid-19 further increase ET-1 expression. While ET-1 may decrease endothelin receptor antagonists inhibit angiotensin II-induced vasoconstriction and lung cell injury.

Angiotensin has been shown to reduce the effects of ET-1 on endothelial cells, especially inflammation and growth (16-18). Administration of treatment with ERAs may include a direct impact on ACE-2 expression and may be advantageous to cope with the treatment of this disease.

Pulmonary fibrosis may develop in Covid-19 patients with ARDS. ET-1 induces differentiation of fibroblast cells into myofibroblastic cell type. ET-1 also triggers the transformation of alveolar epithelial cells into fibroblast-like cells, which contribute to pulmonary fibrosis (32,33). As a result, ERAs have a potential effect in preventing hypoxia in the advanced stages of the disease in the acute lung injury process.

**Nitric oxide (NO):** In ARDS that develops due to COVID-19, pulmonary vasoconstriction probably occurs due to hypoxia triggered by thromboxane A2 and platelet-activating factors. All together these factors limit the pulmonary blood flow to the poorly oxygenated parts of the lungs and make ventilation perfusion (V/Q) mismatch worse, thus contributing to the development of alveolar dead space and hypoxemia. The cumulative consequence of these changes triggers increases in PVR, ultimately leading to pulmonary hypertension and RV dysfunction (34,35).

During the 2003 SARS outbreak, inhaled NO was shown to have antiviral activity against coronavirus. Inhaled NO has been shown to reduce pulmonary hypertension, correct severe hypoxia, and shorten the duration of ventilation support in patients with SARS-CoV compared to control patients (36).

The advantageous effects of NO include particular mechanisms that increase endothelial and smooth muscle relaxation, inhibit platelet aggregation, and prevent direct effects on the immune system. Inhaled NO (iNO) selectively corrects oxygenation and VQ mismatch in ARDS patients without systemic vasodilation. (37-39).

In addition to vasodilation, inhaled NO has many other desirable properties such as bronchodilation, anti-inflammatory and antithrombotic effects, and microbiocidal activity.

The decrease in PVR and the improvement in oxygenation with the betterment of gas exchange induced by iNO, results in an increase in right and left ventricular function and improved cardiac reserve.

**Prostacyclin analogs:** Prostacyclines are drugs commonly used in the treatment of PAH and are similar to endogenous prostacyclin (PGI2). Prostacyclin activates cyclic adenosine monophosphate (cAMP) by binding to the receptor located on the surface of vascular smooth muscle and platelets. This results in inhibition of platelet aggregation, relaxation of vascular smooth muscle, and vasodilation of the pulmonary arteries. In addition, it has cytoprotective and antiproliferative properties.

The effects of prostacyclin in ARDS associated with COVID-19 are exerted through several different mechanisms. Inhaled prostacyclines have been shown to correct VQ mismatch and increase oxygenation in the treatment of ARDS. It can be used to correct life-threatening hypoxemia in treatment-resistant ARDS that can develop in COVID-19 disease (40).

One of the most important complications of COVID-19 disease is hypercoagulability and the resulting micro thrombosis and thromboembolic events in large vessels. Another potential benefit of prostacyclin is to alleviate coagulopathy directly associated with SARS-CoV-2. While allowing platelets to adhere to the damaged vascular tissue and participate in the repair process, prostacyclin also prevents or limits thrombus formation (41).

Prostacyclines also provide a synergistic effect with NO by increasing NO production. **Phosphodiesterase type 5 inhibitors (PDE-5i):** There is strong evidence that PDE-5i inhibitors can reduce harmful effects stemming from overstimulation of the immune system. Through modulating activated T cells, PDE-5i inhibition promotes an anti-inflammatory reaction, reducing cytokine release, increasing oxygen diffusion, decreasing fibrosis and stimulating vascular repair. It may be useful in preventing pulmonary fibrosis, which is a complication of COVID-19 disease (42,43). It should be kept in mind that drugs such
as phosphodiesterase-5 inhibitors or riociguat may decrease blood pressure in patients who are prone to hypotension and considered for intubation.

During the Covid-19 pandemic, the treatment and follow-up protocol of PH patients was interrupted, as in many disease groups. It is essential to evaluate the treatment benefit and the risk of infection due to hospitalization in these patients where follow-up and maintenance of appropriate treatment convey importance. Appropriate clinical examination should be performed by specialized centers in new patients with suspected PH. Many methods used in diagnosis should be postponed due to the high risk of infection. In high-risk patients, diagnostic methods should be applied by taking as appropriate precautions and selectively as possible.

Stable patients with a diagnosis of PH should be followed up by phone or video conference, if possible. Appropriate training programs should be provided to patients and their relatives. PH patients should avoid crowds by staying at home as much as possible. They should wash their hands frequently and should not touch their faces, and should wear a mask in public places to cover their mouth and nose. Current PH medications should not be disrupted. Hospitalization may be required in case of clinical worsening, increased signs of right heart failure, or other complications.

PH drugs should not be discontinued or changed if there is no substantial justification for PH patients who develop COVID-19 disease. Patients who need to be followed up in the intensive care unit, such as severe respiratory infections, should be treated in tertiary care centers if possible. Medical therapy should be adjusted considering drug interactions.

In the most serious pandemic environment that our world has seen since the Spanish flu, our physicians also have an important responsibility to provide the best and most appropriate care for PH patients who are vulnerable and fragile.

References


2. https://www.arcgis.com/apps/opsdashboard/index.html#/bda75947406d4029423467b48e9ecf6/Last Updated at (M/D/YYYY) 2/7/2021


