INTRODUCTION

In December 2019, the first cases of pneumonia of unknown etiology were described in the city of Wuhan and linked to a seafood and wild-animal wholesale market, suggesting at first animal-to-person transmission. Rapidly, human-to-human transmission was confirmed (136), and the virus was isolated and identified as a novel β-coronavirus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (136). Compared with other members of the Coronavirus family, which generally cause mild respiratory disease (111), the SARS-CoV-2-related disease (COVID-19) can lead to severe respiratory disease and death. However, reported mortality rates of 3–4% for SARS-CoV-2 infection appear lower than with SARS-CoV-1 (2002) and the Middle East Respiratory Syndrome (MERS-CoV; 2012), which were associated with case fatality rates of ≈9% (26) and ≈34% (137), respectively (111). Since its first description, the number of COVID-19 cases rose exponentially, rapidly reaching the status of a pandemic causing officially more than 507,000 deaths worldwide as of July 2020.

Interestingly, several viruses have been suspected of leading to the development of pulmonary vascular diseases over the years. The association between human immunodeficiency virus (HIV) infection and severe pulmonary hypertension (PH), with features identical to those seen in patients with idiopathic pulmonary arterial hypertension (PAH), was recognized early on in the AIDS epidemic (110). Although its specific role in PAH pathogenesis remains controversial, the human herpesvirus 8 (HHV-8) genome and HHV-8-encoded latency-associated nuclear antigen 1 were documented in plexiform lesions of patients with PAH (17, 22). However, other studies have since failed to demonstrate this association (15, 62, 86, 119). Research on SARS-CoV-1, MERS-CoV, and more recently on SARS-CoV-2 suggests these viruses promote endothelial dysfunction, vascular leak, and pulmonary microthrombi (19, 37, 46, 55, 76, 100, 103, 112, 116, 120, 135) through mechanisms such as inflammation, hypoxia, oxidative stress, mitochondrial dysfunction, and DNA damage. Although their consequences

**Am J Physiol Lung Cell Mol Physiol** 319: L277–L288, 2020. First published June 17, 2020; doi:10.1152/ajplung.00195.2020. —In the last few months, the number of cases of a new coronavirus-related disease (COVID-19) rose exponentially, reaching the status of a pandemic. Interestingly, early imaging studies documented that pulmonary vascular thickening was specifically associated with COVID-19 pneumonia, implying a potential tropism of the virus for the pulmonary vasculature. Moreover, SARS-CoV-2 infection is associated with inflammation, hypoxia, oxidative stress, mitochondrial dysfunction, DNA damage, and lung coagulopathy promoting endothelial dysfunction and microthrombosis. These features are strikingly similar to what is seen in pulmonary vascular diseases. Although the consequences of COVID-19 on the pulmonary circulation remain to be explored, several viruses have been previously thought to be involved in the development of pulmonary vascular diseases. Patients with preexisting pulmonary vascular diseases also appear at increased risk of morbidity and mortality. The present article reviews the molecular factors shared by coronavirus infection and pulmonary vasculature defects, and the clinical relevance of pulmonary vascular alterations in the context of COVID-19.

coronavirus; COVID-19; pulmonary vascular diseases; SARS-CoV-1; SARS-CoV-2; vascular remodeling

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on the pulmonary circulation remain unknown, these features are strikingly similar to what is seen in the development of pulmonary vascular disease (56). The present article highlights the molecular features shared by coronaviruses infection and pulmonary vasculature defects, examines the clinical relevance of pulmonary vascular diseases in the context of the COVID-19 pandemic. We also discuss the potential long-term effects of COVID-19 on the pulmonary circulation, as well as their management in light of current evidence.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through searches of PubMed for articles published from January 2000, to June 2020, by use of the terms “ARDS”, “acute respiratory distress syndrome”, “COVID-19”, “heparin”, MERS-Cov”, “pulmonary embolism”, “pulmonary arterial hypertension”, “pulmonary hypertension”, “SARS-CoV-1”, “SARS-CoV-2”, “severe acute respiratory syndrome”, and “thrombosis”. Articles published in English, French, and Chinese resulting from these searches and relevant references cited in those articles were reviewed.

CLINICAL PRESENTATION AND DISEASE SEVERITY

With the number of identified COVID-19 cases increasing worldwide, it has become clear that infected patients may present in a number of ways. The incubation period is 5 days on average, with initial symptoms being observed within 11.5 days in 97.5% of patients (68). However, asymptomatic carriers of the virus may represent up to 18–33% of cases and constitute a challenge because of their potential contribution to the silent spreading of the disease (85). The most common symptoms are fever, cough, dyspnea, myalgia, and fatigue (55, 98), but rhinorrhea, gastrointestinal symptoms, anosmia, and ageusia are also reported. A substantial proportion of patients have abnormal laboratory findings, such as lymphopenia, abnormal liver function tests, as well as elevated inflammatory markers, D-dimers, and prothrombin levels (134). Early observational studies also suggested that virtually all patients had parenchymal abnormalities on computed chest tomography (3). Typical features include multilobar ground-glass opacities and consolidations predominantly involving the posterior and lower lung zones. Interestingly, pulmonary vascular abnormalities were also observed on chest CT (129), where vascular thickening has been significantly associated with COVID-19 compared with non-COVID-19 pneumonia (10).

Despite a majority of patients presenting only mild-to-moderate symptoms, it is estimated that 10–20% will require hospitalization, and 10–40% of them will require intensive care unit (ICU) admission (42). Ultimately, up to 0.3–8% of infected individuals will succumb, most commonly of respiratory failure. The case fatality rate of COVID-19 has differed significantly around the world, being as high as 50% in critically ill patients (128). Increased patient age has repeatedly been shown to be associated with an enhanced risk of mortality (42). However, this association was at least partly explained by a higher prevalence of comorbidities in older individuals, as the age-adjusted relative risk of mortality or ICU admission was 1.6–3.5 for patients with malignancy, chronic obstructive pulmonary disease (COPD), diabetes, or hypertension (42). Of note, the clinical presentation of patients with comorbid conditions was strikingly similar, apart from a higher prevalence of dyspnea on admission (42). Surprisingly, less than 2% of hospitalized patients had self-reported COPD in large-scale cohorts from China. These findings, likely reflecting the lack of awareness or appropriate diagnosis of chronic lung disease in community settings and suggest that respiratory diseases were underdiagnosed, thus limiting the external validity of these early observational studies (42).

SIMILARITIES IN MOLECULAR AND CELLULAR DYSFUNCTIONS OBSERVED IN COVID-19 AND PULMONARY VASCULAR DISEASES

COVID-19 Structure, Function, and Interaction with the ACE2 Receptor

Coronaviruses are positive-stranded RNA viruses named after their crown-shaped appearance when viewed under an electron microscope. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. SARS-CoV-2 cycle starts with the interaction between the viral S protein and its functional receptor from the host cells, the angiotensin-converting enzyme 2 (ACE2) receptor (127). This receptor is present on pneumocytes and macrophages, as well as on the surface of arterial endothelial and smooth muscle cells of virtually all organs, especially the heart, lungs, and kidneys (47). Importantly, the SARS-CoV-2 has a higher affinity for human ACE2 compared with SARS-CoV-1 (124). By binding the ACE2 receptor, SARS-CoV-2 enables the action of “transmembrane protease, serine 2” from the host cells to cut open the viral S protein, allowing for the fusion of viral and cellular membranes (52). Upon entry into the host cells, the viral RNA genome is then translated into two polyproteins and structural proteins in the cytoplasm (92) after which, proteins and RNA are packaged into progeny virions and released to infect more cells.

Maintenance of normal ACE2 levels within the host’s lung appears to be beneficial to combat inflammatory lung disease (60). Indeed, ACE2 hydrolyzes angiotensin II to generate angiotensin 1–7. Angiotensin II contributes to the lung damage observed in acute lung injury or acute respiratory distress syndrome (ARDS) by inducing vasoconstriction, proinflammatory, profibrotic, proapoptotic, and proproliferative phenotype (60). Increased angiotensin II circulating levels potentially resulting from COVID-19-mediated ACE2 downregulation correlate with the viral load and lung injury (74). Interestingly, angiotensin II is also upregulated in pleuropneumonic lesions observed in PAH patients, and circulating levels of angiotensin II correlates with disease severity (65). Experimentally, either inhibiting angiotensin-converting enzyme (ACE), blocking angiotensin receptor, or overexpressing ACE2 reverses adverse pulmonary vascular lesions in PH (102). Despite these experimental results, the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) is not recommended for treatment of PH due to the lack of convincing clinical studies on the efficacy and safety of such drugs (59, 81). However, a recent study documented reduced ACE2 activity in a small cohort of PAH patients (49). The same study reported improvements in pulmonary hemodynamics, oxidative and inflammatory markers in patients treated with recombinant human ACE2 (49). Altogether, these obser-
Proinflammatory Storm and Hypercytokinemia

COVID-19 is also usually associated with lymphopenia and cytokine outburst, including IL-6, IL-1β, IL-2, IL-10, TNF-α, and monocyte chemoattractant protein-1, which correlate with COVID-19 severity (82). A recent meta-analysis reported that the mean concentrations of IL-6 were 2.9-fold higher in patients with complicated COVID-19 compared with those who had an uncomplicated disease course (23). Moreover, a single-arm nonrandomized trial showed that tocilizumab treatment in severe COVID-19 reduced oxygen requirements, improved radiographic abnormalities, and resulted in clinical improvement without serious adverse events or death in most patients (23).

Wilk and colleagues (126) investigated the production of inflammatory cytokines in circulating immune cells from COVID-19 patients. They applied a single-cell RNA sequencing to peripheral blood mononuclear cells of seven hospitalized COVID-19 patients and six healthy controls (126). They reported a profound reconfiguration of circulating immune cells in SARS-CoV-2-infected patients, including a novel B cell-derived granulocyte population in patients with severe acute respiratory failure. Intriguingly, they showed that circulating monocytes and lymphocytes do not express substantial amounts of proinflammatory cytokines, suggesting that circulating leukocytes do not hold a predominant role in the COVID-19-related cytokine storm.

In PAH, increased expression of proinflammatory cytokines also contributes to adverse pulmonary vascular remodeling (39) and predicts survival (109). Mechanistically, cytokines have pleiotropic effects, including promoting an antiapoptotic and proliferative environment by activating several pathways like the JAK/STAT3 signaling (110a). Targeting the proinflammatory cytokines or their downstream effectors may thus minimize both lung damage and pulmonary vascular complications in COVID-19 patients, as suggested in PH preclinical models (91, 123). However, inflammatory cytokines and other components of the inflammatory cascade contribute to the host defense against infection. Thus, targeting cytokine expression in COVID-19 patients should be considered with caution. Consequently, the Centers for Disease Control and Prevention (CDC) advises avoiding the use of JAK inhibitors or interferon in COVID-19 treatments because of the lack of convincing studies on the efficacy and safety of such drugs.

Increased Oxidative Stress and DNA Damage

Reactive oxygen species (ROS) are key signaling molecules that play an important role in the progression of inflammatory disorders (84). In vitro, SARS-CoV-1 is associated with increased ROS production (133). In vivo, severe lung injury and proinflammatory host response are dependent on activation of the oxidative stress machinery in monkeys infected by SARS-CoV-1 (106). Increased intracellular ROS results in oxidative DNA damage (96). Single-strand DNA breaks are normally repaired by base excision repair involving the poly-ADP ribose polymerase (PARP). PARP also works as an antiviral agent through the ADP-ribosylation of the viral genome and inhibition of viral transcripts translation (11). Besides, ADP-ribosylation of the transcription factor NF-κB induces interferon-γ (IFNγ) transcription initiating the IFNγ signaling cascade, which contributes to the immune response against viral infection (30). Coronaviridae encodes for a macrodomain protein with poly (ADP-ribose) glycohydrolase activity, which binds and removes ADP-ribose, annealing the antiviral effects of PARP (40). Moreover, PARP expression is increased in cells infected by SARS-CoV-1 (133) and appears to be critical for viral replication, nucleocapsid assembly, and dissemination by promoting cell death (73). Interestingly, PARP inhibition reduced SARS-CoV-2 replication without an obvious cytopathic effect (36). It is thus reasonable to speculate that clinically available PARP inhibitors might have therapeutic values in COVID-19 patients. Extensive studies have shown that DNA damage signaling and PARP activation similarly promote inflammation and mitochondrial alterations leading to severe pulmonary vascular lesions, and the development of pulmonary vascular diseases, such as PAH (83). These observations led to the first clinical trial investigating PARP inhibitors for PAH (NCT03782818).

Mitochondrial Dysfunction

Proteomic analysis of in vitro models of SARS CoV-1 infected cells showed that 36% of the upregulated proteins were located in the mitochondria (including apoptosis-inducing factor, ATP synthase β-chain and cytochrome-c oxidase) (66). A distinct report showed that cells infected by SARS CoV-1 displayed mitochondrial dysfunction, demonstrated by loss of mitochondrial potential (ΔΨm) (133). The authors observed that SARS-CoV-1 nucleocapsid protein induces mitochondrial-dependent cell apoptosis (increased apoptosis-inducing factor, ATP synthase β-chain, and cytochrome-c oxidase). Interestingly, it appears that SARS-CoV-1 can manipulate the host cell mitochondria and alter mitochondrial function to help evade the host’s innate immunity (103). For example, in vitro infection of cells by SARS-CoV-1 caused mitochondrial elongation by triggering ubiquitination and proteasomal degradation of dynamin-like protein 1, leading to the increase in mitochondrial fission and strong induction of autophagy (103). In parallel, the contribution of mitochondrial dysfunction is widely described as a mechanism involved in adverse pulmonary vascular remodeling observed in human and preclinical models of PH (24).

Despite being associated with coronavirus infections, including SARS-CoV-2, inflammation, oxidative stress, and mitochondrial dysfunction are unspecific manifestations also shared by other infections and hypoxemic processes (6, 7, 12, 13, 63, 107). Further investigations are warranted to better dissect and understand the specific molecular defects associated with SARS-CoV-2 infection.

PULMONARY VASCULAR DISEASE: A COMPLICATION AND A RISK FACTOR FOR COVID-19

In addition to common molecular pathways (Fig. 1), several lines of evidence suggest that COVID-19 specifically impacts the pulmonary circulation.
Hypoxemia and Impaired Hypoxic Pulmonary Vasoconstriction

In healthy adults, hypoxic pulmonary vasoconstriction (HPV) occurs in response to alveolar hypoxia. HPV diverts blood flow from poorly ventilated to well-ventilated alveoli, therefore optimizing ventilation-perfusion matching (108). Importantly, when HPV is compromised, intrapulmonary shunts cause a decrease in oxygenation of the pulmonary venous blood flow, ultimately contributing to poor oxygen delivery, organ dysfunction, and failure. Intriguingly, preliminary reports suggest that severe COVID-19 can present as an atypical form of ARDS with significant dissociation between relatively well-preserved lung mechanics and severe hypoxemia. For example, Guan et al. (41) reported dyspnea in only 19% of 1,099 hospitalized COVID-19 pneumonia patients, despite low PaO₂:FIO₂ ratios, abnormal CT scans, and common requirement for supplemental oxygen. These observations could be explained by impaired HPV but also by the loss of lung perfusion regulation, and pulmonary microthrombi (8, 35, 67). Whether patients with severe COVID-19 have impaired hypoxic pulmonary vasoconstriction remains, however, controversial.

Endotheliitis, Vasculitis, and Angiogenesis

Perivascular lymphocytic inflammation induced by SARS-CoV-2 has been observed in post-mortem studies (1, 120). This endotheliitis and vasculitis provoke severe endothelial injury and, consequently, increase the risk of thrombosis. Ackermann and colleagues (1) compared autopsy findings from seven COVID-19-infected patients, seven influenza A (H1N1)-infected patients with ARDS to 10 uninfected control patients. COVID-19-infected lungs exhibited severe endothelial injury, vascular thrombosis associated with microangiopathy, occlusion of alveolar capillaries, and intussusceptive angiogenesis. Interestingly, SARS-CoV-2 infection is also associated with systemic vasculitis, such as cutaneous vasculitis, which could be related to either the viral infection or to the immune response triggered by SARS-Cov-2 in affected patients (18, 21, 29, 61). Interestingly, Endotheliitis and vasculitis have also been observed in some cases of PAH associated with connective diseases and describe in the advanced stage of the diseases (e.g., grade 6 of the Heath and Edwards classification) (27, 43, 48, 71, 93).

Pulmonary In Situ Thrombosis and Embolism

In COVID-19 cohorts, disseminated intravascular coagulation, a condition characterized by the generation of microthrombi in different organs, including the pulmonary circulation (77), was diagnosed in 11% of the patients overall, including 71% of the nonsurvivors (114). The same group noted pulmonary microthrombi at lung dissection from a critically ill COVID-19 patient. Also, a series of 12 consecutive autopsies showed the presence of venous thromboembolism in 58%, contributing to death in four of them (125). Consistently, high levels of D-dimers were repeatedly shown to be associated with the need for ICU admission and mortality among...
COVID-19 patients (72). This is not surprising since lung coagulopathy is relevant in the pathogenesis of ARDS (89). The cytokine storm and pulmonary microthrombi observed with COVID-19 are thus consistent with the immunothrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation during severe infection (33). Tang and colleagues (113) suggested that the use of anticoagulant therapy with heparin was associated with decreased mortality, especially so in patients with significant sepsis-induced coagulopathy or markedly elevated D-dimer levels. Paranjpe et al. (90) also showed a positive association between systemic anticoagulation and survival in hospitalized patients with COVID-19, requiring mechanical ventilation. On the other hand, Tremblay and colleagues (117) showed no difference in mortality in hospitalized patients already on anticoagulation compared with patients without such treatment. As recognized by the authors, these observational studies are subjected to bias and confounding and thus require further confirmation. Moreover, these beneficial effects could be related to the nonanticoagulant properties of heparin, including its anti-inflammatory (131), antiviral (105), and protective effects on the pulmonary endothelium (57), as well as the overall prevention of venous thromboembolism. Indeed, hospitalized COVID-19 patients are also at higher risk of venous thromboembolism due to their intense inflammatory state (41), elevated hypoxia-inducible transcription factors, increased blood viscosity (45), and immobilization. While initial anecdotal reports described cases of pulmonary embolism diagnosed concomitantly with COVID-19 (25, 129), more recent observational studies suggest that venous thromboembolic events are common among COVID-19 patients hospitalized in the ICU despite systematic thrombosis prophylaxis (64). Poissy and colleagues (94) reported that among 107 consecutive confirmed COVID-19 patients admitted to the ICU from Feb 27 to March 31, 2020, 20.6% experienced pulmonary embolism (PE) within a median of 6 days from ICU admission. Interestingly, in a cohort of 196 patients during the same period in 2019, only 6.1% had PE despite a similar severity score upon admission to the ICU. Between January 1 and December 31, 2019, nearly 8% of patients admitted in the ICU (n = 40) due to influenza suffered from PE (94). The high incidence of PE related to COVID-19 was supported by another study performed in 184 ICU patients, where 31% developed thrombotic complications, which comprised 81% of total thrombotic events (64). In that context, it is recommended that COVID-19 patients receive appropriate thrombosis prophylaxis. However, drug-drug interactions between antiplatelet agents or anticoagulants with investigational COVID-19 therapies should be considered (16). Physicians should also be vigilant for signs of venous thromboembolic events. The efficacy, dosage, and characteristics of patients suitable for high-prophylactic doses or systemic anticoagulation remain to be demonstrated.

**Effects of SARS-CoV-2 on Pulmonary Hemodynamics, Right Ventricular Function, and Myocardial Injury**

Similar to ARDS, patients with severe COVID-19 are expected to exhibit a high prevalence of pulmonary vascular defects, which can lead to PH and subsequent right ventricular (RV) dysfunction (122). In a cohort of 120 consecutive patients with COVID-19, Yuan and colleagues (70) showed that low RV longitudinal strain is a predictor of higher mortality. In a cohort of 110 consecutive patients, Argulian et al. (9) also reported that RV dilation (31% of COVID-19 patients) is associated with increased mortality risk. Consistent with this observation, Fox and colleagues (31) reported a massive RV dilation in 10 patients who died from COVID-19. In addition to the COVID-19-specific pulmonary vascular abnormalities described above, the process of pulmonary hemodynamic alterations in ARDS is multifactorial and involves hypoxia, hypercapnia, vascular compression by pulmonary edema and fibrosis, and ventilator-induced increases in alveolar and intrathoracic pressures (122). Together with this increased afterload, ARDS is associated with increased sympathetic stimulation and hypoxia, resulting in myocardial oxygen imbalance, myocardial depression, as well as an increased risk of infarction, acute RV decompensation, and arrhythmia (79). Importantly, in most influenza pandemics, cardiovascular events surpassed all other causes of mortality, including superimposed pneumonia (78). There is also evidence that MERS-CoV caused acute myocarditis (5). Similarly, acute cardiac injury, manifesting as reduced ejection fraction, and increased troponin and natriuretic peptide levels are observed in 7–22% of admitted patients with COVID-19, and independently associated with a higher case fatality rate (104). Myocardium from patients who died from COVID-19 exhibited scattered individual cell myocyte necrosis (31). Supporting this finding, Sharma and colleagues (101) demonstrated that SARS-CoV-2 can enter and replicate in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), resulting in hiPSC-CM apoptosis and cessation of beating. Consistent with this observation, autopsies of patients who died from SARS-CoV-1 revealed that 35% of heart samples displayed the presence of viral RNA, which, in turn, was associated with reduced ACE2 protein expression (88). Similarly, in a murine model, infection with SARS-CoV-1 also precipitated an ACE2-dependent myocardial infection (88). Thus, as observed for SARS-CoV-1, the expression of ACE2 in the human heart could be a potential mechanism of heart injury among patients infected with SARS-CoV-2 (19). A prospective study of SARS-CoV-1 patients without preexisting cardiac disease also confirmed subclinical diastolic dysfunction in the acute stage of the disease (69). However, whether the cardiac injury in COVID-19 results from direct ACE2-dependent myocardial infection, stress cardiomyopathy, high demand in patients with limited myocardial reserve, or indirect myocardial injury due to secondary cytokine storm and microvascular alterations requires further evaluation (Fig. 2) (44). Similarly, the mechanism of RV dilation and dysfunction is likely multifactorial and may involve an interplay between thrombotic events, hypoxic vasoconstriction, cytokine storm, and direct viral damages on cardiomyocytes or endothelial cells.

**Pulmonary Vascular Disease as a Risk Factor for COVID-19**

The presence of severe PH is associated with poorer outcomes among patients with ARDS (122), secondary RV hemodynamic instability being the leading cause of mortality over hypoxemia (97). In patients with preexisting PH, the RV chronically faces increased afterload, initially resulting in adaptive RV hypertrophy. In many cases, however, the RV progresses inexorably toward a maladaptive phenotype culmi-
nating in RV failure and death. Importantly, infection remains a common cause of superimposed acute RV decompensation among patients with chronic PH (51). As observed for PH patients, increased circulating lactate dehydrogenase (LDH) (54), and high-sensitivity C-reactive protein (hsCRP) (95) can accurately predict 10-day mortality of COVID-19 patients (130). Taken together, it makes little doubt that the present pandemic represents a serious threat for patients with preexisting pulmonary vascular diseases, such as PAH and chronic thromboembolic PH, as well as in patients with significant PH related to comorbid disease, such as left heart and respiratory diseases. Although no comprehensive study to date has evaluated whether COVID-19 occurs more frequently or is more severe in these patients compared with the general population, we surprisingly found no evidence for such association based on a PubMed search on June 1, 2020 (64). This most likely reflects the lack of awareness of preexisting PH in early observational studies. On the basis of the apparent key role of the pulmonary vasculature in COVID-19, indirect evidence suggests that current therapies in PAH targeting the nitric oxide (NO), the endothelin, and the prostacyclin pathways may partially influence the COVID-19 prognosis. Indeed, NO has frequently been considered a protective mediator in viral infection due to its microbicidal function, although it could also potentiate inflammation or promote virus latency (118). While inhaled NO (iNO) treatments showed promising results in a patient with concomitant idiopathic pulmonary arterial hypertension (iPAH) and COVID-19 (132), the utility of iNO in treating respiratory manifestations of COVID-19 needs to be proven and supported by clinical trials. Interestingly, over 20 clinical trials investigating the effect of inhaled NO in COVID-19 are currently ongoing. Similarly, endothelin-1 contributes toward increasing the expression of leukocyte adhesion molecules and promotes the synthesis of inflammatory mediators leading to vascular dysfunction during viral pneumonia (32), whereas prostacyclin regulates both the innate and adaptive immune systems (28). Whether current PAH vasoactive therapies have any protective effects clinically remains however unknown.

PH patients are also at higher risk of poorer outcomes owing to indirect consequences of the current pandemic. Indeed, actions to manage the COVID-19 crisis include the cancellation of all nonemergency services, as well as drastic restriction of interhospital patient transfers and hospital-based outpatient clinics. Moreover, access to laboratories and imaging studies is altered by infection control procedures. Thus, reduced delivery of health care to PH patients is a potential adverse consequence of the global response to control the SARS-CoV-2 pandemic. During other pandemics, such as the influenza outbreaks, increased cardiovascular and other non-influenza-related deaths have been observed due to limited access to care (53). Prolonged and unprecedented containment procedures are expected to be associated with suboptimal patient management.

**PREVENTION AND TREATMENT OF COVID-19 INFECTION IN PATIENTS WITH PULMONARY VASCULAR DISEASES**

In the absence of a vaccine or approved therapies against SARS-CoV-2, preventive measures currently remain the best strategy for COVID-19 in patients with pulmonary vascular...
COVID-19 is a global pandemic evolving in real time that is associated with significant morbidity and mortality. Lungs remain the organ mostly affected by SARS-CoV-2 infection, leading to severe respiratory disease in many individuals. Patients with preexisting comorbid conditions, including patients with pulmonary vascular diseases, are at particularly high risk of hospitalization and death. While the effects of COVID-19 for the pulmonary circulation are being defined, several lines of evidence suggest that the molecular features of SARS-CoV-2 infection are strikingly similar to what is seen in pulmonary vascular disease development, promoting endothelial dysfunction, lung coagulopathy and microthrombi, and hemodynamic impairments (Table 1). The involvement of the pulmonary vasculature is also supported by imaging studies. While there are a number of treatments under investigation, pathologic assessments and long-term studies assessing the risk of developing chronic pulmonary vascular lesions following COVID-19 are needed to inform on the putative ongoing vascular remodeling effects of COVID-19 and best long-term management of survivors.

Table 1. Similarities between COVID-19 and pulmonary hypertension

| Symptom                  | COVID-19 | PH |
|--------------------------|----------|----|
| Dyspnea                  | +++      | +++|
| Fatigue                  | +++      | +  |
| Inflammation             |          |    |
| Endotheliitis            | +++      | +* |
| Vasculitis               | +++      | +  |
| Myocarditis              | +        | −  |
| Proinflammatory cytokines| ↑↑↑↑     | ↑↑ |
| Thrombosis, microthrombi |     ↓↓↓↓|   ↑|
| D-dimers                 | ↑        |   |
| Prothrombin              | ↑↑↑      |   |
| DNA damage               | ↑        |   |
| PARP                     | ↑        |   |
| RAA activation           | ↓↓↓↓     |   |
| ACE 2                    | ↓        |   |
| Angiotensin 2            | ↑↑↑      |   |
| Cardiac injury           |          |    |
| Ejection fraction        | ↑↑↑↑     |   |
| Troponin                 | ↑↑       |   |
| Natriuretic peptide      | ↑↑       |   |
| RV dilatation            | ↑↑↑↑     |   |
| Pulmonary vascular thickness | ↑↑↑↑ |   |
| Mitochondrial dysfunction| ↑↑↑↑     |   |
| ROS                      | ↑↑↑↑     |   |
| Endothelial dysfunction  | ↑↑↑↑     |   |
| HPV                      | ↑↑↑↑     |   |

HPV, hypoxic pulmonary vasoconstriction; PARP, poly-ADP ribose polymerase; PH, pulmonary hypertension; RAA, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; RV, right ventricle. *Occasionally; †group 1 pulmonary hypertension; ‡group 2 pulmonary hypertension; §group 3 pulmonary hypertension. ↑ increased, ↓ decreased, + observed, ++ generally observed, ++++ frequently observed.
COVID-19 infection will be of great interest for both basic and clinical research.

NOTE ADDED IN PROOF

On June 15, 2020, after this article was accepted, the FDA revoked the emergency use authorization (EUA) that allowed for chloroquine or hydroxychloroquine to be used to treat hospitalized patients with COVID-19 when a clinical trial was unavailable or participation in a clinical trial was not feasible (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and). This decision reflects the lack of beneficial effects of these medications for decreasing the likelihood of death or speeding recovery in large clinical trials and the serious cardiac adverse events associated with chloroquine or hydroxychloroquine treatment.

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AUTHOR CONTRIBUTIONS

F.P. prepared figures; F.P., V.M., M.L., S.M., A.C.L., O.B., S.B., and S.P. edited and revised manuscript; F.P., V.M., M.L., S.M., E.B.-G., A.C.L., O.B., S.B., and S.P. edited and revised manuscript; F.P., V.M., M.L., S.M., A.C.L., O.B., S.B., and S.P. approved final version of manuscript.

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