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COVID-19 and the pulmonary vasculature

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Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) present in a number of ways, from asymptomatic carriers to respiratory failure with acute respiratory distress syndrome (ARDS)-like features. Early observational studies documented that virtually all hospitalized patients had parenchymal abnormalities on computed chest tomography. Interestingly, vascular thickening was also shown to be a predominant imaging finding in COVID-19 compared to non-COVID-19 pneumonia (observed in 59% vs. 22%, $p < 0.001$),[1] implying a potential tropism of the virus for the pulmonary vasculature. This is not surprising since its functional receptor from the host cells, the angiotensin-converting enzyme 2 receptor, is largely present on the surface of pulmonary vascular cells. Accordingly, diffuse endothelial inflammation, dysfunction and apoptosis resulting from direct viral infection of the endothelial cells have been reported within the lungs and other organs. Several lines of evidence also suggest that COVID-19 impacts the pulmonary circulation clinically. For example, patients with severe COVID-19 commonly present an atypical form of ARDS with significant dissociation between relatively well-preserved lung mechanics and severe hypoxemia for which the loss of hypoxic vasoconstriction lung perfusion regulation has been proposed as a possible explanation.[2] Systematic assessment of thrombotic complications also revealed a high incidence of confirmed venous thromboembolic events amongst patients hospitalized in the ICU, likely exacerbating ventilation–perfusion mismatch.[3] Disseminated intravascular coagulation, a condition characterized by the generation of microthrombi in different organs including the pulmonary circulation, was also diagnosed in 71% of the non-survivors of COVID-19, and pulmonary microthrombi were observed at lung dissection from critically ill COVID-19 patients. Consistently, high levels of D-dimers were repeatedly shown to be associated with mortality amongst COVID-19 patients in line with the immuno-thrombosis model of severe sepsis and ARDS, and anticoagulant therapy with heparin has been reported to be associated with decreased mortality, especially so in patients with significant sepsis-induced coagulopathy or markedly elevated D-dimer levels.[4] Whether these observations could be related to the non-anticoagulant properties of heparin, including its anti-inflammatory, antiviral, and protective effects on the pulmonary endothelium remains elusive. Given the increased risk of bleeding and previous negative trials of endogenous anticoagulants in sepsis, this retrospective study requires further validation before the efficacy and best dosage, as well as characteristics of patients most suitable for systemic anticoagulation beyond the traditional prevention and management of venous thromboembolism are confirmed.

Similar to ARDS in which pulmonary hypertension (PH) is common and negatively impacts outcomes, patients with severe COVID-19 are expected to exhibit a high prevalence of PH acutely. Accordingly, the present pandemic likely represents a serious threat for the vulnerable group of patients with pre-existing severe chronic PH. In these patients, the right ventricle (RV) chronically faces increased afterload, initially resulting in adaptive RV hypertrophy. In many cases, however, the RV progresses inexorably towards a maladaptive phenotype culminating in RV failure and death. Importantly, infection remains one of the commonest reasons precipitating acute RV decompensation amongst patients with chronic PH. Although no comprehensive study to date has evaluated whether COVID-19 occurs more frequently or is more severe in these patients compared to the general population, we found no evidence for such association based on a PubMed search on 12 May 2020.

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This most likely reflects the lack of awareness of pre-existing PH in early observational studies. Nonetheless, based on the apparent key role of the pulmonary vasculature in COVID-19, current therapies for pulmonary arterial hypertension (PAH) may specifically influence the effects of the COVID-19 on the pulmonary circulation and the lungs, as recently speculated.[5] Indeed, nitric oxide has microbicide function, whereas endothelin-1 plays a role in the increased expression of leukocyte adhesion molecules and the synthesis of inflammatory mediators contributing to vascular dysfunction during viral pneumonia, and prostacyclin regulates both the innate and adaptive immune systems.

In the absence of a vaccine or approved therapies against SARS-CoV-2, preventive measures and optimal PH guideline-oriented therapies undoubtedly remain the best strategy for COVID-19 in patients with severe PH. In any case, however, PH patients appear at higher risk of poorer outcomes due to indirect consequences of the COVID-19 pandemic. Current actions to control the COVID-19 include the cancellation of all non-emergency services, and an almost complete curtailment of hospital-based outpatient clinics. Consequently, access to physicians, laboratories and imaging studies are frequently limited by infection control procedures. While there is little debate regarding the necessity of a concerted response to control the COVID-19 outbreak, these unprecedented containment procedures may, if prolonged, be associated with suboptimal management and healthcare delivery to PH patients that may ultimately result in poorer outcomes. This is not unique to COVID-19, as several studies documented increased cardiovascular and non-influenza-related deaths during influenza outbreaks, either related to the infection itself or the limited access to care.

As the world progressively recovers from the acute stages of the pandemic, we may also be facing new challenges regarding the long-term consequences of COVID-19 on the pulmonary circulation. As can be extrapolated from data on ARDS and SARS-CoV-1, survivors of severe COVID-19 may experience persistent impairment in pulmonary gas exchange. While frequently attributed to mild restrictive patterns commonly observed in these patients, impaired diffusing capacity may also partly be of vascular origin. Indeed, several viruses have been directly linked to the development of chronic pulmonary vascular diseases in the past, including the human immunodeficiency virus infection. Research on the SARS-CoV-1 (2002), the Middle East Respiratory Syndrome (MERS-CoV; 2012), and more recently, the COVID-19 also documented that molecular features observed with these infections (e.g. inflammation, oxidative stress, DNA damage) share similarities to those seen in pulmonary vascular disease development, including PAH. The COVID-19 could thus promote persistent pulmonary vascular defects and subsequent PH development, especially in patients with persistent lung impairment post-COVID-19 or susceptible patients with genetic predisposition or chronic lung and heart diseases. Although its long-term consequences remain unknown, the assessment of the effects of COVID-19 on the pulmonary circulation, both acutely and chronically, will thus be of great interest for both basic and clinical research.

Authors' contribution

All the authors (SP, FP and SB) have written and edited the article. Accordingly, each coauthor:

1. Made substantial contributions to the article.
2. Drafted sections of the article and revised it critically.
3. Provided final approval of the version to be published.
4. Agreed to be accountable for all aspects of the article.

Conflict of interest

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