Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 patients may become predisposed to pulmonary arterial hypertension

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A B S T R A C T

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing the current pandemic of coronavirus disease 2019 (COVID-19) that have killed over one million people worldwide so far. To date, over forty million people have officially been identified to be infected with this virus with less than 3% death rate. Since many more people are expected to have been infected with this virus without the official diagnosis, the number of people who have recovered from the SARS-CoV-2 infection should be substantial. Given the large number of people recovered from either the mild SARS-CoV-2 infection or more severe COVID-19 conditions, it is critical to understand the long-term consequences of the infection by this virus. Our histological evaluations revealed that patients died of COVID-19 exhibited thickened pulmonary vascular walls, one important hallmark of pulmonary arterial hypertension (PAH). By contrast, such pulmonary vascular remodeling lesions were not found in patients died of SARS-CoV-1 during the 2002–2004 SARS outbreak or due to the infection by H1N1 influenza. The advancement in the treatment for the human immunodeficiency virus (HIV) infection has been remarkable that HIV-infected individuals now live for a long time, in turn revealing that these individuals become susceptible to developing PAH, a fatal condition. We herein hypothesize that SARS-CoV-2 is another virus that is capable to triggering the increased susceptibility of infected individuals to developing PAH in the future. Given the large number of people being infected with SARS-CoV-2 during this pandemic and that most people recover from severe, mild or asymptomatic conditions, it is imperative to generate scientific information on how the health of recovered individuals may be affected long-term. PAH is one lethal consequence that should be considered and needs to be monitored. This may also foster the research on developing therapeutic agents to prevent PAH, which has not so far been successful.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded RNA virus that is currently causing the pandemic of coronavirus disease 2019 (COVID-19) [1,2]. Millions of people have been infected with SARS-CoV-2 worldwide, and COVID-19 continues to cause serious health, economical, and sociological problems. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as a receptor to enter the host cells [3,4], and some infected individuals develop severe pneumonia and acute respiratory distress syndrome (ARDS) [5]. So far, over one million people have died because of COVID-19. It has been noted that elderly patients with systemic hypertension and other cardiovascular diseases are particularly susceptible to developing severe and possibly fatal conditions of COVID-19 [1,6,7], highlighting the importance of vascular effects of this virus.

While it is currently widely considered that treating lung and cardiovascular aspects of COVID-19 is the key for reducing the severity of COVID-19 and the associated mortality, it is unclear exactly how the SARC-CoV-2 infection affects patients. Thus, understanding the effects of SARS-CoV-2 and COVID-19 on the cardiovascular/pulmonary system should help develop therapeutic strategies to reduce the mortality associated with COVID-19. Furthermore, long-term consequences of being infected with SARS-CoV-2 after the recovery are unknown. As this is a novel pathologic condition, new information are generated every day as we progress through this pandemic. Even if effective vaccines and therapeutics are developed, long-term consequences that may result in adverse health outcomes in the future in millions of affected individuals cannot be overlooked.

Pulmonary arterial hypertension (PAH) affects both females and males of any age, in which the increased pulmonary vascular resistance causes right heart failure and death [8,9]. The median survival for patients diagnosed with PAH has been reported to be 2.8 years from the time of diagnosis (3-year survival: 48%) if untreated [10,11]. Even with currently available therapies, only 58–75% of PAH patients survive for 3 years [12–15]. While the exact mechanism of how PAH is developed is unknown, this condition is associated with various conditions including viral infections such as HIV.[9] HIV-associated PAH occurs with a prevalence of approximately 1 out of 200 HIV-infected individuals

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[16–19] that is 100 to 500-times higher than the prevalence of PAH in people without HIV infection. Findings from a large prospective study of 7,648 HIV patients showing a prevalence of 0.5 percent was performed in 2004 and 2005 after the antiretroviral therapy (ART) was introduced [17] and were similar to those studies of HIV-PAH performed before the ART. Thus, the ART does not seem to have altered the prevalence of HIV-PAH, providing evidence for the direct role of the viral infection in promoting the pathogenesis of PAH.

The hypothesis

We hypothesize that *SARS-CoV-2 possesses mechanisms that promote the pathogenesis of PAH and that some individuals infected with this virus become susceptible to developing clinically significant PAH in the future*. The hypothesis is based on clinical observations that certain viral infections are associated with the development of PAH and our recent finding that patients died of COVID-19 exhibit the histological signs of thickened pulmonary vascular walls. Thus, it is logical to hypothesize that at least a subset of SARS-CoV-2 infected patients are predisposed to developing severe PAH in the future, and we herein encourage research activities to specifically evaluate this concept in order to reduce more people dying as a consequence of the current pandemic.

Evaluation of the hypothesis

As SARS-CoV-2 causing the COVID-19 pandemic, we collected lung samples from patients died of COVID-19 in Ukraine and compared with archived samples of patients who died of H1N1 influenza. Pulmonary arteries of COVID-19 patients consistently exhibited histological characteristics of the vascular wall thickening [20]. By contrast, pulmonary vessels of patients who died because of the H1N1 influenza infection did not show thickened pulmonary arteries. Lung histology images published earlier of patients died of ARDS during the 2002–2004 SARS outbreak due to the infection with SARS-CoV-1 by Hwang et al. [21] and Ding et al. [22] did not show the signs of thickened pulmonary vascular walls. We performed a morphometric analysis of the pulmonary vessels of patients died of infections with SARS-CoV-2 and H1N1 influenza virus and found that the pulmonary arterial walls of COVID-19 patients was more than 2-fold thicker than those of patients with H1N1 influenza [20]. We also noted the occurrence of pulmonary arterial wall thickening in lung histology images of patients who died of COVID-19 in China although authors did not mention this in their papers [5,23].

These observations in deceased patients infected with SARS-CoV-2, SARS-CoV-1 and H1N1 influenza viruses indicate that pulmonary vascular wall thickening is a unique feature of the SARS-CoV-2 infection and COVID-19. As deceased COVID-19 patients consistently exhibit pulmonary vascular wall thickening, this condition may play a vital role in the development of acute respiratory failure. These results also lead us to hypothesize that some patients who recovered from COVID-19 may be predisposed to developing PAH and right-sided heart failure.

While knowing whether the individuals previously infected with SARS-CoV-2 develop PAH or not need to await case reports and epidemiological studies that may not become available for years to come, we may be able to generate information that could be useful for reducing adverse health outcomes through the use of experimental animals. Experimental animals that are infected with SARS-CoV-2 virus or treated with SARS-CoV-2 viral components [20] may develop the characteristics of PAH and pulmonary vascular remodeling and/or may enhance the sensitivities of the trigger for PAH such as hypoxia and SU5416 [24,25].

Consequences of the hypothesis

Such information generated in experimental animals in conjunction with human patient case reports as well as epidemiological studies may suggest that some individuals who were previously infected with SARS-CoV-2 have tendencies to develop PAH. The increased susceptibilities to develop PAH may only occur in those patients who survived severe COVID-19 or may also occur in those who developed mild or even no symptoms in response to the SARS-CoV-2 infection. While currently there are no agents that are known to prevent the development of PAH, new research motivated by this situation may allow for obtaining effective measures to cope with this unwanted health crisis. Hopefully, our hypothesis is proven to be wrong, however, it is critical to be aware of such a possibility.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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