

# The overlooked chamber in coronavirus disease 2019

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## Abstract

Coronavirus disease 2019 (COVID-19) causes a pandemic around the globe. Debilitating and even deadly complications have occurred to the millions. A recent study reported 31% of right ventricular dilation in the hospitalized COVID-19 patients, which is significantly associated with the mortality. Therefore, we sought to search for the lines of evidence in the literature that COVID-19 may contribute to right heart dysfunction. The relevant literature and data from PubMed, Embase, Cochrane Library databases, and Web of Science were searched using the MeSH terms including 'COVID-19', 'SARS-CoV-2', 'novel coronavirus pneumonia', 'novel coronavirus', 'right heart failure', 'right heart dysfunction', 'pulmonary hypertension', 'pulmonary embolism', and various combinations. The collected literature and data were sorted and summarized. Literature reports that angiotensin-converting enzyme 2 (ACE2) is the host receptor mediating the cell entry of severe acute respiratory syndrome coronavirus 2. Clinical and experimental evidence shows that loss of function of ACE2 aggravates pulmonary hypertension and gain of function of ACE2 exerts protection on cardiopulmonary circulation. Moreover, the patients with COVID-19 are more susceptible to pulmonary embolism and severe pneumonia-induced acute respiratory distress syndrome. Therefore, COVID-19 may cause right heart dysfunction by inducing pulmonary hypertension, pulmonary embolism, and acute respiratory distress syndrome. Particular attention should be paid to the function of the right heart, the overlooked chamber in COVID-19. Blood gas analysis, laboratory test of cardiac injury markers, physical examination, and echocardiography should be performed to identify right heart failure as early as possible. Once the right heart failure is confirmed, the therapeutic modalities following the guidelines of European Society of Cardiology should be employed to reduce mortality.

**Keywords** COVID-19; SARS-CoV-2; Right heart failure; Right heart dysfunction; Pulmonary hypertension; Pulmonary embolism

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## Introduction

The novel coronavirus has rapidly spread throughout the world, causing pneumonia and severe complications in the infected people. For instance, 61.1% of the patients with coronavirus disease 2019 (COVID 19) developed acute respiratory distress syndrome (ARDS), 26.1% were transferred to the intensive care unit (ICU), and 41.7% received non-invasive and 47.2% invasive ventilation in the ICU.<sup>1</sup> Moreover, cardiac

injury occurred in 19.7% of the patients with COVID-19,<sup>2</sup> thereby leading to the high risk of in-hospital mortality. However, the right heart function, which could play an important role under the diseased condition, has been rarely reported. Recently, a retrospective study demonstrated that right ventricular (RV) dilation was observed in 31% of the hospitalized patients with COVID-19, which is significantly associated with the mortality.<sup>3</sup> Herein, we summarize several lines of evidence that COVID-19 may contribute to right heart dysfunction.

## The roles of angiotensin-converting enzyme 2 in coronavirus disease 2019 and pulmonary hypertension

Angiotensin-converting enzyme 2 (ACE2), a multifunctional protein, is the host receptor through which severe acute respiratory syndrome coronavirus 2 enters cell and triggers infection.<sup>4,5</sup> ACE2 is expressed in the central nervous system, blood vessels, lungs (alveolar epithelial cells and pulmonary endothelial cells), heart, and gastrointestinal tracts of humans.<sup>6,7</sup> Loss of function of ACE2 in these tissues causes circulatory and vascular abnormalities. For instance, loss of ACE2 in brain stem facilitates to increase sympathetic tone, alter baroreflex, and exacerbate hypertension. Moreover, reduced expression of ACE2 in vasculature induces endothelial dysfunction and inflammation, as well as aggravates existing atherosclerosis and diabetic vasculopathy. Importantly, loss of ACE2 in the lungs exacerbates hypertension and induces respiratory distress and fibrosis post-viral infection; a decreased ACE2 activity is associated with bleomycin-induced pulmonary fibrosis and pulmonary hypertension (PH).<sup>8</sup> On the contrary, activated ACE2 and its downstream signalling may indicate a compensatory or protective mechanism launched by the distressed organism. For example, ACE2 levels in the circulating endothelial cells of the PH patients are significantly higher than the healthy controls; higher ACE2 activity with increased angiotensin-(1–7) levels has been reported in heart ventricles of the patients with primary PH,<sup>9</sup> indicating a cardiopulmonary protective role for ACE2.<sup>10</sup> Additionally, activation of ACE2 alleviates PH in rats; thus, ACE2 can be a promising therapeutic target for PH.<sup>11,12</sup>

Therefore, ACE2 is central to pulmonary endothelial function and lung pathophysiology. Although there is no direct clinical evidence showing the influence of COVID-19 on PH,<sup>13</sup> taking into account for the previously mentioned clinical indirect evidence and experimental evidence, the patients with COVID-19 suffering from refractory hypoxaemia and/or elevated N-terminal pro-BNP and/or heart failure should be cautiously monitored.

## Coronavirus disease 2019 and pulmonary embolism

The incidence of pulmonary embolism (PE) in patients with COVID-19 may be high,<sup>14–18</sup> which is attributed to hypoxaemia, systemic inflammation, activation of coagulating cascades, and prolonged bed rest associated with COVID-19.<sup>19</sup> According to a recent study, 10 hospitalized COVID-19 patients with RV enlargement were examined by computed tomography angiography of the chest, and five of them showed evidence of PE.<sup>3</sup> However, PE could be

underdiagnosed because of non-specific symptoms largely overlapping with those of COVID-19.<sup>20</sup> Hence, PE should be suspected in the patients with COVID-19 under the scenarios, such as unexpected respiratory worsening, new/unexplained tachycardia, a dramatic fall in blood pressure not attributable to tachyarrhythmia, hypovolaemia or sepsis, (new-onset) electrocardiogram changes suggestive of PE, and deep vein thrombosis of lower extremities. If acute PE is confirmed, the therapeutic strategies should be guided by risk stratification according to the current guidelines issued from the European Society of Cardiology.<sup>21</sup>

## Severe coronavirus disease 2019 pneumonia and right heart dysfunction

Circulatory failure is common in ARDS and is an independent risk factor of death, which could be ascribed to RV failure-related ARDS, also known as acute cor pulmonale (ACP) and accounting for 50% of the ARDS patients with circulatory failure.<sup>4</sup> Ventilatory strategy, ventilator-associated pneumonia, and septic cardiomyopathy can contribute to ACP. Also, the injury to pulmonary circulation inherent to the diseased condition and high positive end-expiratory pressure should not be ignored, which promotes the uncoupling between RV and pulmonary circulation and then facilitates RV failure.<sup>22</sup> Indeed, 22% of the patients with moderate to severe ARDS have been reported to progress to ACP in the ICU, with poor outcomes from severe cases.<sup>23</sup> Notably, Argulian and colleagues showed that out of 110 consecutive hospitalized patients with COVID-19, 31 (30%) patients were intubated and mechanically ventilated, and 32 (31%) patients presented with RV dilation at the time of echocardiographic examination. Moreover, there were 13 (41%) deaths with RV dilation in the 21 COVID-19 patients succumbed to death.<sup>3</sup>

## Early diagnosis of right heart failure in coronavirus disease 2019 patients

It is possible that COVID-19 causes right heart dysfunction by PH, PE, severe pneumonia, ventilator usage, and sepsis, which may be associated with high mortality. The mechanism of RV failure is likely multifactorial and includes thrombotic events, hypoxaemic vasoconstriction, cytokine milieu, and direct viral damage. Right ventricular dilation was strongly associated with in-hospital mortality in these patients. Therefore, it is imperative for physicians to pay attention to right heart function in the hospitalized patients with COVID-19, particularly the COVID-19 patients suffering from severe pneumonia, ARDS, and those subjected to ventilator strategy. Right heart failure (RHF) should be considered when the COVID-19

patients in ICU or with ventilator presented with refractory hypoxaemia and/or elevated cardiac injury biomarkers including troponin, brain natriuretic peptide, and N-terminal pro-BNP.<sup>24</sup> In addition, physical examinations are conducive to identifying the COVID-19 patients with RHF. The presence of a high jugular venous pulse, peripheral oedema, and a parasternal heave is suggestive of severe PH.<sup>25</sup> Finally, echocardiography and computed tomography are necessary to evaluate the right heart functions in the COVID-19 patients with suspected RHF. The most common indexes of right heart function include tricuspid annular plane systolic excursion, the size of the right ventricle and right atrium, the ratio of the right heart to left heart, the reflux of contrast media to inferior vena, and the inferior vena cava collapse rate.<sup>21,26</sup>

## Therapeutic strategies for the coronavirus disease 2019 patients with right heart failure

Once RHF is confirmed in the COVID-19 patients, the therapeutic strategies should be based upon the European Society of Cardiology guidelines. The treatment modalities of RHF include trigger removal, volume optimization, ventilator parameter modification, vasopressor and inotrope treatment, and mechanical circulatory support.<sup>26,27</sup> One should keep in mind that systemic vascular resistance should be greater than that in pulmonary vessels by administering systemic vasopressor such as noradrenaline and that RV afterload be reduced by

pulmonary vasodilators including epoprostenol and nitrous oxide inhalant.<sup>13,28</sup> For the severe COVID-19 patients with ARDS, right heart catheterization should be performed to evaluate and monitor right heart functions and haemodynamics.

Taken together, the right heart plays a crucial role in COVID-19 patients, which, however, is often ignored. Respiratory physicians and cardiologists should pay attention to this overlooked chamber under the condition of COVID-19, vigilantly monitoring RV performance and left ventricular filling of the patients, thereby reducing mortality and improving quality of life under COVID-19 pandemic.

## Conflict of interest

None declared.

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