Review Article

Pulmonary Circulation

In the eye of the storm: the right ventricle in COVID-19

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Abstract

The corona virus disease of 2019 pandemic caused by the SARS-CoV-2 virus continues to inflict significant morbidity and mortality around the globe. A variety of cardiovascular presentations of SARS-CoV-2 infection have been described so far. However, the impact of SARS-CoV-2 on the right ventricle is largely unknown. Due to its pathophysiologic relevance, the right ventricle finds itself in the eye of the storm of corona virus disease of 2019, placing it at higher risk of failure. Increased afterload from acute respiratory distress syndrome and pulmonary embolism, negative inotropic effects of cytokines, and direct angiotensin converting enzyme 2-mediated cardiac injury from SARS-CoV-2 are potential mechanisms of right ventricle dysfunction in corona virus disease of 2019. Early detection and treatment of right ventricle dysfunction may lead to decreased mortality and improved patient outcomes in corona virus disease of 2019.

Keywords

acute respiratory distress syndromes (ARDSs) and acute lung injury, COVID-19, pulmonary embolism, pulmonary hypertension, right ventricle function and dysfunction

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Introduction

The novel corona virus disease of 2019 (COVID-19) has resulted in significant morbidity and mortality across the globe. The mortality from SARS-CoV-2 infection is mainly attributed to acute respiratory distress syndrome (ARDS) and fatal cardiovascular complications. In fact, mortality is markedly higher in COVID-19 patients with myocardial injury than those without (59.6% vs. 8.9%).[1] Clinically, there are a variety of cardiovascular presentations of SARS-CoV-2 infection including cardiac ischemia, decompensated heart failure, arrhythmias, and cardiogenic shock.[2,3] It is not clear whether these cardiovascular presentations are provoked directly by SARS-CoV-2 or indirectly by cytokine- or stress-induced myocardial dysfunction. Interestingly, a retrospective study of COVID-19 patients with evidence of respiratory distress showed signs of pulmonary hypertension (PH) with mild decrease in Tricuspid annular plane systolic excursion, though no significant difference in right ventricle (RV) size was noted.[4] However, a recent study did show that non-survivors of COVID-19 without known cardiomyopathy had RV dilation, diminished RV function, and elevated pulmonary arterial systolic pressure.[5] This study demonstrated that evaluation of RV function should be considered as a predictor of mortality in COVID-19 patients.[5] Given the physiological relationship between RV and pulmonary vasculature, we suspect that RV dysfunction and failure is contributing to the rapid hemodynamic deterioration, arrhythmias, and sudden cardiac death in patients with COVID-19. Here, we identified potential causes of acute RV dysfunction in the setting of SARS-CoV-2 infection.

Acute respiratory distress syndrome

ARDS is one of the major complications in hospitalized patients with COVID-19 (Fig. 1). A recent retrospective study showed development of ARDS in 23.3% of

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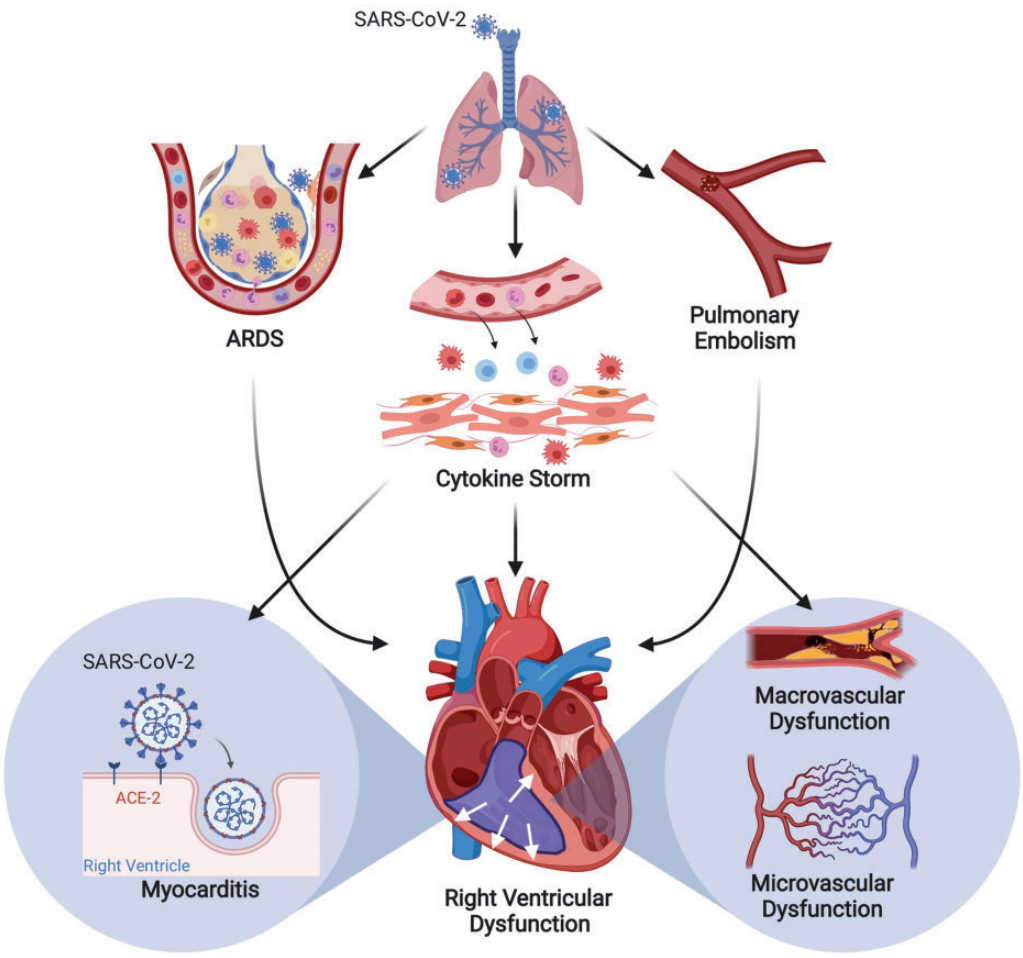

Fig. 1. Plausible mechanisms of development of right ventricular dysfunction in COVID-19. Schematic showing development of right ventricular dysfunction from COVID-19-associated acute respiratory distress syndrome (ARDS), pulmonary embolism, cytokine storm, micro- and macrovascular dysfunction, and direct angiotensin-converting enzyme 2 (ACE2)-mediated effects of SARS-CoV-2 virus on the right ventricle.
Note: Figure created with BioRender.com

hospitalized patients, of which 58.5% had underlying cardiac injury.[6] RV dysfunction is frequently associated with moderate to severe ARDS and is one of the major determinants of mortality.[7] In fact, RV dysfunction was found to be an independent predictor of mortality in moderate to severe ARDS patients.[7–9] The development of RV failure in the setting of ARDS is mainly attributed to the increased pulmonary vascular resistance (PVR) from increased vasoactive mediators, vascular remodeling, hypoxic pulmonary vasoconstriction, intravascular thrombosis, and vascular compression from atelectasis and edema.[6] Since most ARDS patients require positive pressure ventilation (PPV), the uncoupling between the RV and pulmonary circulation under PPV can also contribute to RV failure. Interestingly, recent autopsy reports from COVID-19 patients with severe ARDS showed evidence of RV dilatation.[10,11] Thus, it is plausible that the thin-walled RV is particularly susceptible to ischemia and dysfunction in response to sudden increases in afterload and/or coronary occlusion by microthrombi (further discussed below), which in turn may compromise left ventricular function.

Pulmonary embolism (PE)

Recent reports have demonstrated an increased incidence of pulmonary thromboembolism (PE) in COVID-19 patients,[12] predisposing them to acute RV failure[13] (Fig. 1). The hemodynamic response of the RV to acute PE depends on the size of embolus, degree of obstruction, physiologic response to released vasoactive compounds, and baseline cardiopulmonary status. RV failure is considered the principal determinant of early mortality in acute PE, and thus early detection of RV dysfunction and myocardial injury is paramount. The mechanism of RV dysfunction in the setting of PE involves increased afterload from acutely elevated PVR secondary to localized hypoxic pulmonary vasoconstriction and release of vasoactive substances.[14,15] In regards to COVID-19 patients, there are increasing reports showing marked dysregulation of coagulation pathways as evidenced by elevated d-dimer and fibrin degradation products, prolonged prothrombin time, and thrombocytopenia in COVID-19 patients.[16,17] In fact, a recent autopsy study showed higher incidence of deep vein

thrombosis and pulmonary embolism in COVID-19 patients.[18] Similar thrombotic complications have also been reported in patients with SARS-CoV and Middle East Respiratory Syndrome infection.[19] Lung autopsies from patients with SARS-CoV infection revealed thromboemboli in pulmonary, bronchial, and small lung veins.[19] In addition, the severe inflammatory response in ARDS can lead to diffuse microthrombi formation within pulmonary vasculature.[20,21] Emerging evidence in severe COVID-19 patients with ARDS identified a pattern of tissue damage consistent with complement-mediated thrombotic microvascular injury in the lung.[22] Thus, we suspect that the formation of microthrombi within the pulmonary vasculature due to the imbalance of coagulation and inflammatory pathways in ARDS increases the risk of thromboembolic complications and subsequent RV dysfunction in COVID-19 patients.

Myocarditis

Myocarditis has been reported as a possible cause of acute myocardial injury and heart failure in COVID-19 patients,[23] although the underlying mechanism is still unclear. Autopsy reports, albeit limited, have shown either biopsy-proven lymphocytic myocarditis in the absence of pulmonary symptoms,[24] scattered myocyte necrosis with no significant lymphocytic infiltration in myocardium of COVID-19 patients,[10] or mononuclear infiltrates consisting of lymphocytes in the RV of a COVID-19 patient.[18] In addition, a recent study identified pericytes as the site of SARS-CoV-2 infection, which may lead to capillary endothelial cell and microvascular dysfunction.[25] Altogether, these findings suggest direct injury to cardiomyocytes and pericytes in a fraction of COVID-19 patients may lead to acute myocarditis. Acute myocarditis is a known cause of new onset RV failure through either direct involvement of RV and/or LV via elevated PVR. Currently, it is unclear whether the inflammatory infiltrates and/or myocyte degeneration/necrosis involves specifically the RV and/or LV given the limited biopsies.

Angiotensin converting enzyme 2 (ACE2) has been implicated in the direct cardiac effects of SARS-CoV-2 and is highly expressed in different heart cells (pericytes, cardiomyocytes, fibroblasts, endothelial cells).[25] ACE2 is known to convert angiotensin II (Ang-II) into Ang (1–7), which is considered a counter-regulatory axis of the renin angiotensin aldosterone system (RAAS) that can attenuate vasoconstriction, cell proliferation, fibrosis, and inflammation. Recent studies have demonstrated ACE2 as the key determinant of SARS-CoV-2 viral entry. SARS-CoV-2 likely leads to a loss of ACE2-mediated anti-inflammatory and protective effects in the heart.[26] In fact, the transmembrane protease serine 2-primed SARS-CoV-2, after entering into cardiac cells via ACE2, may induce tumor necrosis factor (TNF)-α converting enzyme (TACE/A Disintegrin and Metalloproteinase-17 (ADAM-17))-mediated shedding of ACE2 to its soluble form, resulting in a shift toward increased ACE/Ang-II-mediated pro-inflammatory effects in the RV.

Micro- and macro-vascular dysfunction

The combination of endothelial/pericyte dysfunction and ACE/Ang-II pro-inflammatory effects may possibly explain the increased incidence of COVID-19-associated coagulopathy that appears to mimic disseminated intravascular coagulation without adverse bleeding.[27] A recent study identified septal capillary injury accompanied by extensive deposition of complement C5b-9, C4d, and mannan-binding lectin serine protease-2 in the lung.[22] Another study noted endothelial cell involvement across multiple vascular beds in COVID-19 patients.[11] Since endothelial cells and pericytes express ACE2, it is possible that COVID-19 can lead to complement-mediated endothelial and microvascular injury in the heart. If so, this could lead to accumulation of inflammation that may result in vasculitis and/or disruption of vascular homeostasis by increasing vessel hyper-permeability, vasospasms, perfusion defects, and subsequent ischemia, thus, resulting in an imbalance between oxygen supply and demand, which is a known precipitant of RV dysfunction.

The involvement of SARS-CoV-2 in macrovascular diseases is unclear. Pneumonia and influenza infection have been associated with an increased risk of acute myocardial infarction (MI), especially in patients with pre-existing cardiovascular disease.[28–30] Previous studies have demonstrated a significant increase in inflammatory cells in atherosclerotic coronary arteries during an acute systemic infection.[31–33] The increase in circulating inflammatory cytokines causes an activation of inflammatory cells embedded in atherosclerotic plaques, which leads to coronary plaque destabilization and subsequent myocardial ischemia. It is possible that direct SARS-CoV-2 infection of endothelial cells and/or indirect release of circulating cytokines could lead to coronary plaque destabilization. Thus, patients with history of coronary artery disease and/or risk factors for atherosclerotic cardiovascular disease could possibly be at a higher risk for developing coronary ischemia in the setting of SARS-CoV-2 infection. Even though Guo et al. reported no evidence of acute MI on admission from COVID-19 patients,[1] the combination of high fever or hypoxia due to lung disease with coronary plaque instability may still result in type II myocardial ischemia. Interestingly, a case study from a patient without known cardiovascular risk factors developed an acute MI from an in-situ thrombotic stenosis of the proximal right coronary artery.[34]

Cytokine storm

Cytokine storm is common in COVID-19 patients and comprises an array of inflammatory cytokines that exert pleiotropic effects on the immune system (Fig. 1). Serum levels of one such cytokine interleukin 6 (IL-6) correlate with respiratory failure, ARDS, and adverse clinical outcomes.[25,35,36] SARS-CoV-2 infection in the RV is expected to increase the release of vasoactive peptides and induce RAAS imbalance to promote myocardial recruitment of inflammatory cells and is speculated to activate T cell-mediated adaptive

responses.[37,38] On the contrary, Li et al. proposed that SARS-CoV-2 could directly infect T-lymphocytes and initiate/promote their death that may eventually lead to lymphopenia and impeded anti-viral responses.[39] It is speculated that the sustained and substantial reduction in CD4 + and CD8 + T helper cell subtypes[40] and hypoxia-induced excessive intracellular calcium may result in cardiomyocyte apoptosis in COVID-19 patients.[41] Cardiac myofibroblasts and cardiomyocytes act as a key source of a wide array of pro-inflammatory cytokines including IL-6 and are highly responsive to IL-6, IL-1β, and TNFα. Furthermore, prolonged/excessive synthesis of IL-6 is reported to induce cardiac hypertrophy, fibrosis, and diastolic dysfunction.[37] The plethora of pro-inflammatory cytokines involved in developing the cytokine storm can also contribute to RV dysfunction through their negative inotropic effects on the myocardium.[42] Taken together, the depressed RV contractility may prove to be fatal in the face of acutely elevated PVR from ARDS and pulmonary embolism in COVID-19.

Pulmonary hypertension

SARS-CoV-2 may worsen RV function in the presence of pre-existing chronic right heart failure conditions. For example, PH is the most common cause of RV failure. Currently, there are limited reports on SARS-CoV-2 infection in PH patients.[43] However, numerous studies have demonstrated the involvement of ACE2 in PH and ARDS. ACE2 is expressed in the lung epithelial cells and pulmonary vascular cells, and recent evidence suggests it's critical role in maintaining pulmonary function.[26,44] The current evidence includes, but is not limited to the following: (1) ACE2 knock-out in mice exacerbates ARDS,[45] pulmonary congestion and heart failure,[46] and chronic hypoxia-induced PH[47]; (2) lung ACE2 expression is down-regulated in PH[48,49] and fibrosis[50]; (3) increased circulating levels of Ang-II and ACE2, but reduced ACE2 enzymatic activity[51] in pulmonary arterial hypertension (PAH) patients; (4) administration of recombinant ACE2 attenuates lipopolysaccharide-induced ARDS[52]; and (5) overexpression of ACE2 by lentivirus[53] and administration of ACE2 agonists attenuates preclinical models of PH.[54] These studies among others have supported the fundamental concept that lung ACE2 is protective against various pulmonary diseases, but the role of ACE2 in the RV remains unclear. Previous studies have shown improvement of RV function secondary to PH by modulation of the RAAS system with ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonist.[53,55–58] In addition, administration of recombinant ACE2 can improve RV function and diminish RV hypertrophy[57] in an experimental PH model.

There is increasing evidence that the immune system plays a pivotal role in the pathogenesis of PH. For instance, patients with idiopathic PAH have substantial increase in perivascular mast cells, macrophages, dendritic cells, and T-cells.[59] Inflammatory cytokines and chemokines can contribute to the pathogenesis of PH by recruiting immune cells, activating and proliferating pulmonary arterial smooth muscle cells, and causing endothelial cell dysfunction. Interestingly, direct administration or over-expression of IL-6 can lead to PH,[60–62] whereas loss of IL-6 attenuated hypoxia-induced PH and RV hypertrophy.[60] Clinically, elevated levels of IL-6 have been reported in idiopathic PAH patients.[61] Also, a recent study showed an independent inverse relationship between serum IL-6 levels and RV function in PH patients,[63] though the underlying mechanism is unclear.

Given the involvement of ACE2 and pro-inflammatory state in PH patients, we suspect that patients with PH are at an increased risk for RV dysfunction and failure in the setting of SARS-CoV-2 infection. It is plausible that RV function can easily decompensate by precipitating factors such as stress of an acute infection (fever, tachycardia) and ARDS in PH patients as a consequence of imbalance between increased metabolic demand and reduced cardiac reserve. The presence of compensatory RV hypertrophy in patients with pre-existing PH is meant to reduce wall stress in a high afterload state. However, the sudden increase in RV afterload with the development of severe ARDS/hypoxemia and/or reduction in effective RV function by direct myocardial injury/infarction may contribute to poor outcomes in these patients. The reported increased in circulating levels of IL-6 in COVID-19 may also contribute to RV dysfunction in PH patients.

Finally, experimental and clinical studies suggest baseline ACE2 deficiency in PH. We speculate that ACE2 down-regulation by SARS-CoV-2 in patients with baseline ACE2 deficiency in the lung may further enhance the ACE/Ang-II-Angiotensin II receptor type I (pro-inflammatory) axis. This can increase expression of TACE/ADAM-17 by Ang-II, promote shedding of membrane-bound ACE2 and reduce its activity, and consequently lead to further loss of ACE2/Ang (1–7) protective effect. The imbalance between ACE/Ang-II and ACE2/Ang (1–7) axis can facilitate the progression of inflammation/cytokine storm, worsening PVR, and hypercoagulable state in pre-existing lung disease. Also, ACE2 is highly expressed by type II pneumocytes in the lung, which produces alveolar surfactant and serve as progenitor cells of type I pneumocytes. Thus, injury to type II pneumocytes from SARS-CoV-2 binding of ACE2 could lead to alveolar collapse and impaired gas exchange, inflammation, and fibrosis.

Long-term consequences from COVID-19 infection

COVID-19 may lead to long-term detrimental effects in the lungs and heart, particularly in critically ill patients. A 12-year longitudinal study of patients who recovered from SARS reported abnormal lipid metabolism (68%), cardiovascular abnormalities (44%), and altered glucose metabolism (60%).[64] Also, the development of pulmonary fibrosis in SARS-CoV and ARDS patients during recovery, and animal models of SARS have been reported.[65]

Given SARS-CoV-2 affinity for lung and heart tissues, it is possible that a cohort of recovered patients may sustain long-lasting injury to heart and lung. Based on these studies, severe lung injury in the setting of SARS-CoV-2 infection may lead to pulmonary fibrosis, elevated pulmonary pressures, cardiovascular disease, and altered metabolism after recovery. These are all risk factors for the development of RV failure. Long-term follow-up of cardiopulmonary function will be necessary for COVID-19 patients, and further investigation of RV dysfunction should be considered.

Current knowledge gaps in RV related research in COVID-19

RV dysfunction and failure are recognized complications of various cardiac and pulmonary disorders, which are associated with poor prognosis. Given the recent evidence of RV involvement in COVID-19 patients, addressing the following knowledge gaps could be crucial in advancing our understanding of RV function in COVID-19 patients: (1) right heart catheterization and echocardiography data from large, multicenter COVID-19 patient cohorts; (2) circulating pro-inflammatory and coagulation system biomarkers and their correlation with right ventricular dysfunction; (3) electrophysiologic evidence for the involvement of right ventricular arrhythmias to COVID-19-related mortality; (4) detailed histopathologic studies of the right ventricular and pulmonary vascular autopsy tissue from COVID-19 patients; and (5) molecular and biochemical analysis of right ventricular tissue and pulmonary vasculature and further characterization of ACE2, ADAM-17, and soluble ACE2 expression and function in COVID-19.

Conclusion

In conclusion, the unique pathophysiology of COVID-19 places the RV at higher risk of failure. Elevated PVR from ARDS and pulmonary embolism, negative inotropic effects of cytokines, microvascular and macrovascular dysfunction, and direct ACE2-mediated cardiac injury from SARS-CoV-2 are potential mechanisms of RV dysfunction in COVID-19. More research is needed to understand the precise molecular mechanisms of RV pathology in COVID-19. Early detection and treatment of RV dysfunction can lead to decreased mortality and improved patient outcomes in COVID-19.

Conflict of interest

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