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Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 1568–1572

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Editorial

# The Right Ventricle in COVID-19 Lung Injury: Proposed Mechanisms, Management, and Research Gaps

CORONAVIRUS DISEASE 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is a complex multisystem disorder primarily characterized by pulmonary involvement.[1] Although lung injury leading to acute severe respiratory failure is the most feared clinical presentation of COVID-19, cardiac complications in patients without underlying heart disease also could be a feature of the syndrome and range from 20% to 30%.[2-4] Right ventricular (RV) dysfunction (RVD) seems to be particularly common (20%-39%) in the COVID-19 patient group and often remains undiagnosed.[5,6] RVD is present when the functional and structural variables to quantify RV function are less than the lower value of the normal range: RV fractional area change <35%, RV ejection fraction <45%, tricuspid annular plane systolic excursion <17 mm, and pulsed-Doppler S wave <9.5 cm/s. RV fractional area change has been used to classify the degree of RVD as mild (25%-35%), moderate (18%-25%), and severe (<18%).[7,8]

## Pathophysiology of RVD in COVID-19

### *COVID-19 Coagulopathy and the Right Ventricle*

Like previous virulent zoonotic coronavirus outbreaks, COVID-19 may predispose patients to hemostatic abnormalities, including disseminated intravascular coagulation and thrombotic events.[9,10]

The most characteristic finding of COVID-19 coagulopathy seen in nonsurvivors with COVID-19 is diffuse alveolar damage accompanied by extensive microvascular thrombosis in the lungs and other extrapulmonary sites.[11] The multisystem involvement can be explained by binding of a surface glycoprotein on SARS-CoV-2 (commonly referred to as the "spike protein") to angiotensin-converting enzyme 2 receptors, expressed not only by vascular endothelial cells but also by epithelial cells in the lungs, heart, kidney, and intestine.[12]

The entry of the virus contributes to inflammation and damage of the endothelial cells, causing release of plasminogen activator, which explains the high D-dimer concentration in severe cases, and prothrombotic mediators, primarily factor VIIIc and von Willebrand factor multimers. The latter mediate the consequent deposit of microvascular thrombi, especially in affected pulmonary vessels.[13-15]

The simultaneous presence of vascular inflammation and coagulopathy might explain the high incidence of thromboembolic complications in patients with COVID-19. Similarly, markers of coagulopathy, such as D-dimer, have been closely associated with thrombotic complications and increased mortality.[13,16-18]

Pulmonary hemodynamic alteration created by intravascular microthrombosis and vasoconstriction secondary to hypoxia may cause acute pulmonary hypertension, resulting in suboptimal RV-pulmonary arterial (PA) coupling (a determinant of RV systolic pressure and RV stroke volume) and secondary RVD in patients with COVID-19, even at the early stages of the disease.[19,20] In the critically ill patient with COVID-19, adaptation of the right ventricle to increased loading conditions may be limited because of systemic hypotension and inflammation, and, as a result, RVD can progress to RV failure.[19,20]

### *Myocardial Injury in COVID-19*

Early reports from China identified the presence of elevated cardiac biomarkers in a considerable proportion of patients with COVID-19.[3,21] Specifically, increased troponin and brain natriuretic peptide levels were shown to be correlated with elevation in D-dimer and were predictive of poor outcomes.[22] Recent studies have reported cardiac complications, such as acute coronary syndromes, cardiac arrhythmias, myocarditis, pericarditis, and heart failure, in nearly 20% of patients with COVID-19, which are associated with an increased risk of death.[21] However, it remains unclear whether RVD in the presence of myocardial complications without microvascular or macrovascular pulmonary thrombosis is caused by RV ischemia, RV-PA uncoupling, or severe inflammation.[23]

https://doi.org/10.1053/j.jvca.2021.01.014

*COVID-19 Sepsis and Effect on the Right Ventricle*

Although severe COVID-19 infection shares many laboratory and clinical features of severe bacterial sepsis, up to 80% of patients with COVID-19 may have no microbiologic evidence of bacteremia or fungemia.[24,25] However, added severe intensive care unit−acquired infections potentially can complicate the clinical course of COVID-19 critically ill patients, leading to multiple organ dysfunction and death. Can viral sepsis explain RVD in COVID-19 "lung-injured" patients? In theory, isolated RVD in patients with sepsis reflects endothelial dysfunction, altered vasoreactivity, acute increase in pulmonary vascular resistance despite systemic vasodilation, inability of the right ventricle to adapt to physiologic stress, and it is associated with long-term mortality.[26-28] This mechanistic link, however, is yet to be proven in prospective COVID-19 studies.

*Impaired Gas Exchange and Injurious Invasive Ventilation*

Hypoxemia and/or hypercapnia with or without acidemia in COVID-19 patients with severe acute respiratory failure may cause or exacerbate pulmonary vasoconstriction, resulting in increased (even modest) RV afterload, RV-PA uncoupling, and RVD, with potential for reduced cardiovascular performance.[23,29,30]

"Injurious" invasive ventilation in COVID-19 patients with refractory hypoxemia and/or hypercapnia with extremes of tidal volume, high transpulmonary (alveolar plus pleural) pressure and driving (plateau pressure − total positive end-expiratory pressure [PEEP]) pressures, and excessive PEEP causing non-physiologic lung "stress" and "strain" and alveolar overdistention may result in alveolar vessel collapse and an acute increase in PVR, leading to RVD.[31-33]

In patients with acute respiratory distress syndrome (ARDS), the following one clinical and three physiologic parameters have been identified as statistically significant predictors of RVD: (1) lower respiratory tract infection as a cause of pulmonary ARDS, (2) ratio of arterial oxygen partial pressure to fractional inspired oxygen ratio $<150$ mmHg; (3) partial pressure of carbon dioxide $\geq 48$ mmHg, and (4) driving pressure $\geq 18$ $cmH_2O$.[34] A RVD risk score $> 2$ is associated with a 19% incidence of RVD (followed by 34% and 74% for risk scores of 3 and 4, respectively). Although this scoring system makes physiologicasense, it has not been validated in COVID-19 patient populations.[34] However, it highlights the importance of "RV-protective" ventilation strategies in patients with "injured" lungs and the need for early echocardiography.

## Echocardiography Features of RVD in COVID-19 and Outcomes

Although the diagnostic approach to suspected RVD should be multimodal, echocardiography remains the cornerstone bedside tool to assess cardiac function and pathology. A large prospective echocardiography study of COVID-19 patients showed that even though RV dilation with or without dysfunction was the most common abnormality (39%), followed by left ventricular (LV) diastolic dysfunction (16%), LV systolic impairment was uncommon. Twenty percent of patients in that cohort experienced a deterioration of the RV parameters, probably secondary to increased pulmonary vascular pressure contributing to increased RV afterload.[6] Similar results were demonstrated in a more recent retrospective echocardiography study that evaluated 110 patients.[35] In that cohort, although LV function and size were normal, RV dilation was present in 31% of patients. More than half (66%) of the latter group had RV hypokinesia, and 21% had moderate or severe tricuspid regurgitation.[35] In another small retrospective study that included invasively ventilated patients with COVID-19, 42.2% of whom received venovenous extracorporeal membrane oxygenation (VV-ECMO), found radial RV impairment with sparing of longitudinal function to be the dominant echocardiographic phenotype.[36]

Two-dimensional speckle-tracking echocardiography also has been used to evaluate RV function in COVID-19 patients, and, interestingly, RV longitudinal strain was identified as a powerful predictor of mortality.[37] There is a clear need for large-scale prospective echocardiography data in COVID-19 patients at risk of RVD in order to identify early markers of dysfunction, characterize the natural history of RVD, and monitor response to therapies.

## Management of RVD in Invasively Ventilated COVID-19 Critically Ill Patients

The principles of RVD management in patients with COVID-19 should follow standard general RVD management, including optimization of RV preload, increase in RV contractility, and reductions in pulmonary vascular resistance and RV afterload, leading to optimal RV-PA coupling.[38] Importantly, "RV-protective" strategies should be implemented early, and rescue-specific therapies, such as extracorporeal membrane oxygenation (ECMO), should be considered in refractory selected cases in centers with expertise in the use of ECMO for cardiorespiratory support.[38]

## RV Protection and Prevention of Additional RV Injury

*Invasive Mechanical Ventilation*

The debate on how to ventilate patients with COVID-19 is still ongoing. A number of inter-related editorials have suggested that a subset of patients with COVID-19−induced ARDS has an unusual physiologic phenotype ("L-type" phenotype), with low elastance, low lung weight, and low recruitability. Based on these physiologic results, the authors suggested that high levels of PEEP may be detrimental and that prone positioning is unlikely to be beneficial.[39]

A recent study suggested that patients with early severe COVID-19 pneumonitis did not differ in their response to high PEEP and prone positioning from classic ARDS and,

therefore, should be ventilated according to established ARDS principles and regimens.[40]

Protective ventilation in ARDS reduces RVD and, specifically, a plateau pressure <26-to-28 $cmH_2O$ is associated with lower incidence of RVD. Despite the possible presence of distinct phenotypes of COVID-19 patients with severe respiratory failure, currently there is a lack of data relating to the best "RV-protective" ventilatory strategies.[41] It would stand to reason that in patients with or at risk of RVD, an "RV-protective" ventilatory strategy should comprise the following[42-44]: (1) low "stress" ventilation (plateau pressure <27 $cmH_2O$ and driving pressure <18 $cmH_2O$); (2) partial pressure of carbon dioxide <48 mmHg; (3) arterial oxygen partial pressure-to-fractional inspired oxygen ratio >150 mmHg; (4) consideration of driving pressure–guided PEEP titration (aiming for a PEEP range associated with lowest driving pressure); and (5) consideration of echocardiography use (transthoracic or transesophageal) during PEEP titration to monitor RV loading conditions.[42-44]

### *Prone Ventilation*

Prone ventilation has the potential to recruit collapsed alveoli and reduce tidal hyperinflation, alveolar cyclic recruitment and de-recruitment, and ventilator-induced lung injury known to exacerbate RVD.[45-47] Correction of hypoxemia and hypercapnia reduces pulmonary vasoconstriction, thus unloading the right ventricle in ARDS.[45-48]

So far, no data are available on the effects of prone positioning on RVD (assessed with echocardiography) and pulmonary circulation in COVID-19 patients.[48] Given the "RV-protective" effect of prone positioning, it could be hypothesized that COVID-19-ventilated patients with RVD potentially would benefit from early prone positioning, irrespective of the degree of hypoxemia; however, this notion needs to be tested in prospective studies.

### *Pulmonary Vasodilators*

Although current evidence does not support the routine use of pulmonary vasodilators and, in particular, inhaled nitric oxide (iNO) in patients with ARDS, because it does not confer survival benefit, its use as a rescue therapy has been recommended by recently published guidelines on the management of acutely ill COVID-19 patients with severe respiratory failure.[49]

Pulmonary vasodilators theoretically could be beneficial in selected patients through an improvement in ventilation-perfusion matching through their vasodilatory effect and subsequent reductions in pulmonary arterial pressure and RV afterload.[50] In a recent case report, iNO was administered to a patient with RVD and COVID-19 pneumonitis requiring VV-ECMO to improve the recirculation fraction by reducing pulmonary hypertension, RV afterload, and tricuspid regurgitation.[49] In that patient, iNO successfully offloaded a pressure-overloaded right ventricle and reduced the severity of tricuspid regurgitation and recirculation 12 hours after initiation of therapy.[49]

The role of other pulmonary vasodilators, such as inhaled prostanoids and analogs (prostacyclin and iloprost, respectively) and phosphodiesterase-5 inhibitors (sildenafil) in COVID-19, is unknown and should be used with caution given the lack of data and potential for worsening of hypoxemia and shunt fraction.[38,51]

Future research should focus on the potential benefit of early use of pulmonary vasodilators and inodilators (eg, phosphodiesterase-3 inhibitors) in critically ill COVID-19 patients with RVD confirmed with echocardiography or right-sided heart catheterization.

### *ECMO*

VV-ECMO improves hypoxemia and reduces hypercapnia, facilitating a "lung-rest" strategy, with tight control of driving pressure, and, ultimately, can decrease pulmonary vasoconstriction and RV afterload.[52]

Contrary to preliminary results from early studies that indicated dismal outcomes in COVID-19 patients supported with VV-ECMO, recent studies have demonstrated an estimated <40% probability of 60-day mortality, similar to those treated with ECMO in the ECMO to Rescue Severe Lung Injury in Severe ARDS (EOLIA) trial.[52,53]

Because of the significant incidences of RV dilation and dysfunction in severe COVID-19, traditional VV-ECMO may not be effective, and a change in strategy to support the right ventricle may be required. This may be achieved by either venoarterial (VA), VV, veno-venous arterial (V-VA), or veno-pulmonary arterial ECMO.[53-55]

The conventional VA-ECMO mode has obvious hemodynamic advantages (RV unloading, peripheral oxygenation, temperature control) but carries several disadvantages. For example, patients may present with an increased LV afterload, leading to insufficient unloading and requiring an additional LV venting device, especially if there is coexisting LV impairment. A recent observational cohort study of the Extracorporeal Life Support Organization database demonstrated increased mortality associated with the use of VA-ECMO in patients with COVID-19.[53] Cardiac ECMO, however, was used in a small proportion of patients only (3%), and this may suggest that it was provided as a salvage therapy to patients at the extreme end of disease severity.

V-VA-ECMO has the advantage of providing respiratory support and biventricular cardiac support. The right ventricle is decompressed, and the RV afterload is reduced because of oxygenated and decarboxylated blood flowing through the pulmonary circulation. Currently, there is a paucity of data to suggest that this strategy is beneficial in COVID-19 patients with RVD.

A direct PA cannulation approach accessed either surgically or percutaneously to facilitate venopulmonary arterial ECMO has been suggested to unload and support the failing right ventricle while providing respiratory support.[54] A recent study documented the use of a single-access, dual-stage cannula in a group of patients with COVID-19 requiring VV-ECMO support. This approach demonstrated multiple advantages,

including direct pulmonary artery flow, negligible recirculation, and early extubation and mobilization during ECMO support, with a survival rate of 73%.[55] This might be the way forward to support the right ventricle in COVID-19 patients with RVD and refractory severe respiratory failure requiring extracorporeal support and in whom pharmacologic and ventilatory "RV-protective" measures fail. However, this was a single-center study, and, therefore, larger, multicenter trials would be required to demonstrate that these outcomes can be replicated. In addition, strategies to simplify and improve access to safe percutaneous PA cannulation would facilitate more widespread use of this technique.

## Conclusion

The right ventricle is intricately connected to the clinical syndrome resulting from SARS-CoV-2 infection. In less-severe states, the right ventricle is able to compensate to ensure normal physiology; however, in decompensated states, this leads to severe manifestations of the disease. As a result, RVD is associated with worse outcomes in the context of COVID-19.[35,56] This remains very difficult to manage, and future research should be directed at ways of protecting the right ventricle before dysfunction develops, monitoring of RVD and response to treatment, echocardiographic and hemodynamic RVD phenotyping, and effective management of established RV failure in patients with severe COVID-19.

## Conflict of Interest

V.Z. is founder and chair of PRORVnet.

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