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Editorial

Protecting the Injured Right Ventricle in COVID-19 Acute Respiratory Distress Syndrome: Can Clinicians Personalize Interventions and Reduce Mortality?

THE ABNORMAL INTERACTION between the right ventricle (RV) and pulmonary vasculature in various disease states is associated with adverse clinical outcomes.[1] Impaired RV physiology in acute respiratory distress syndrome (ARDS) is a major determinant of mortality.[1] Right ventricular and pulmonary vascular dysfunction are particularly prevalent in patients with ARDS secondary to coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 infection.[2-4] In this issue of the *Journal of Cardiothoracic and Vascular Anesthesia,* Paternoster et al[5] sought to determine if echocardiographic evidence of deranged RV and/or pulmonary vascular physiology is associated with mortality in patients with COVID-19 ARDS. The authors performed a systematic review and meta-analysis of nine high-quality observational studies (n = 1,450), reporting on mortality in patients with COVID-19 with acute respiratory failure and echocardiographic evidence of RV dysfunction and/or RV dilatation and/or pulmonary arterial hypertension (PAH).[5] Right ventricular dysfunction and dilatation were defined according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines, and PAH was defined using the European Society of Cardiology and European Respiratory Society criteria.[6,7] Abnormal function and/or dimensions of the RV, as well as PAH, were found to be major determinants of mortality.[5]

Mechanistic Links—The Need for a Broad Definition?

There is clearly an association between abnormal RV and pulmonary vascular physiology and adverse outcomes in patients with COVID-19 with acute respiratory failure,[5] but what are the mechanistic links and how should one define abnormal RV/PA physiology to capture and treat pathologies that lead to mortality and potentially identify targets of therapeutic interventions and RV phenotyping?

Understanding RV biomechanics and, in particular, the relationship between the RV and PA is key to identifying different phases of RV dysfunction leading to RV failure and death. RV-PA coupling is determined by end-systolic and pulmonary arterial elastance (E_{es} and E_a, representing RV contractility and afterload, respectively).[8,9] In acute PAH states, RV contractility increases to maintain RV-PA coupling and the E_{es}:E_a ratio between 1.5-to-2 (homeometric mechanism).[8,9] In patients with COVID-19 ARDS, the presence of systemic inflammation, microvascular thrombosis, hypercapnia, hypoxemia, and acidemia, as well as high driving pressure and mechanical power in those requiring invasive ventilation, result in worsening PAH, reduction in the E_{es}:E_a ratio (<1), and RV dilatation to maintain flow (heterometric adaptation).[8,9] As Paternoster et al[5] stated in their systematic review, there is also a possibility that in patients with COVID-19 with severe disease, high levels of proinflammatory cytokines exert a direct negative inotropic effect on the RV. The resultant RV-PA uncoupling leads to the inability of the RV to meet the flow demands without excessive use of the Frank-Starling mechanism, and systemic congestion ensues.[8-10] It has become apparent that both loading conditions and direct insult to the RV can adversely affect outcomes. In this editorial, the authors are using "RV injury" as an umbrella term that encompasses one or more of the following echocardiographic RV phenotypes: RV dilatation, RV dysfunction, Acute Cor Pulmonale (ACP), and Acute PAH. This potentially could enable clinicians to better characterize the spectrum of RV pathology, individualize therapies, and systematically protect the RV; however, this notion must be confirmed and validated in prospective studies.

In the meta-analysis by Paternoster et al, approximately 50% of patients were invasively ventilated.[5] Data on utilization rates of prone ventilation; noninvasive ventilation; continuous positive airway pressure or high-flow nasal oxygen, including duration and level of support; and failure rates were not available. Data relating to the use of extracorporeal membrane oxygenation (ECMO), ventilatory parameters, and

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pulmonary mechanics, such as driving pressure, positive end-expiratory pressure, and mechanical power (known to adversely affect RV-PA coupling when they exceed certain thresholds), also were not provided.[1,5] It would be important to explore mechanisms of refractory RV injury in COVID-19 despite "RV-protective" measures (eg. veno-venous ECMO, low stress and/or strain-invasive ventilation, prone ventilation), and whether there is a link between noninvasive respiratory support and potential patient self-inflicted lung injury and 'RV-injury' in spontaneously breathing patients with COVID-19.[11]

Can We Protect the "Injured" Ventricle and Prevent Further Injury?

Early Diagnosis and Real-Time Monitoring

Given the effect COVID-19 ARDS has been shown to have on the pulmonary vascular physiology, it is fundamental that signs of early RV injury are identified and protective strategies are introduced with the goal of individualizing therapies and preventing RV failure.

Two-dimensional echocardiography remains the most widely used tool to assess RV function in critical illness.[12] It is essential in assessing the RV geometrics, myocardial function, and hemodynamic data and can reliably identify RV chamber dilatation and evidence of impaired systolic function. Conventional parameters, such as tricuspid annular plane systolic excursion, tissue Doppler imaging-derived systolic velocity, and fractional area change (FAC) all have data to support their use in RV systolic assessment.[6] Right ventricular diastolic dysfunction is common in patients with ARDS in the absence of RV dilatation; it is, therefore, important to consider that increases in pulmonary vascular resistance will also adversely affect diastolic function, possibly earlier than that demonstrated on systolic assessment.[13] Assessment of RV diastolic function (morphologic assessment of the inferior vena cava, Doppler interrogation of tricuspid inflow, tissue Doppler at the lateral tricuspid annulus, and pulsed-wave Doppler sampling of hepatic vein flow) should be considered and included in future clinical prediction models determining RV injury risk in ARDS.[14]

A recent observational study exploring myocardial phenotypes and clinical associations of RV dysfunction in COVID-19 ARDS showed that severe COVID-19 ARDS is associated with a specific phenotype characterized by radial impairment with sparing of longitudinal function.[15] Longitudinal parameters, such as tricuspid annular plane systolic excursion, RV systolic velocity, and RV free wall strain, identified significantly fewer patients with RV dysfunction than when used with RV velocity time integral and RV FAC, an important reminder that a complete dataset, including both static and dynamic data, is needed to fully evaluate the RV in this subset of patients.[15] In the same study, RV-PA coupling expressed as an FAC:RV systolic pressure ratio was found to provide additional information above standard RV performance measures.[15]

An important consideration is the frequency when echocardiographic assessment is performed. Measurements derived from a single echocardiogram provide only a snapshot of the RV size and function. It is of the opinion of the authors that

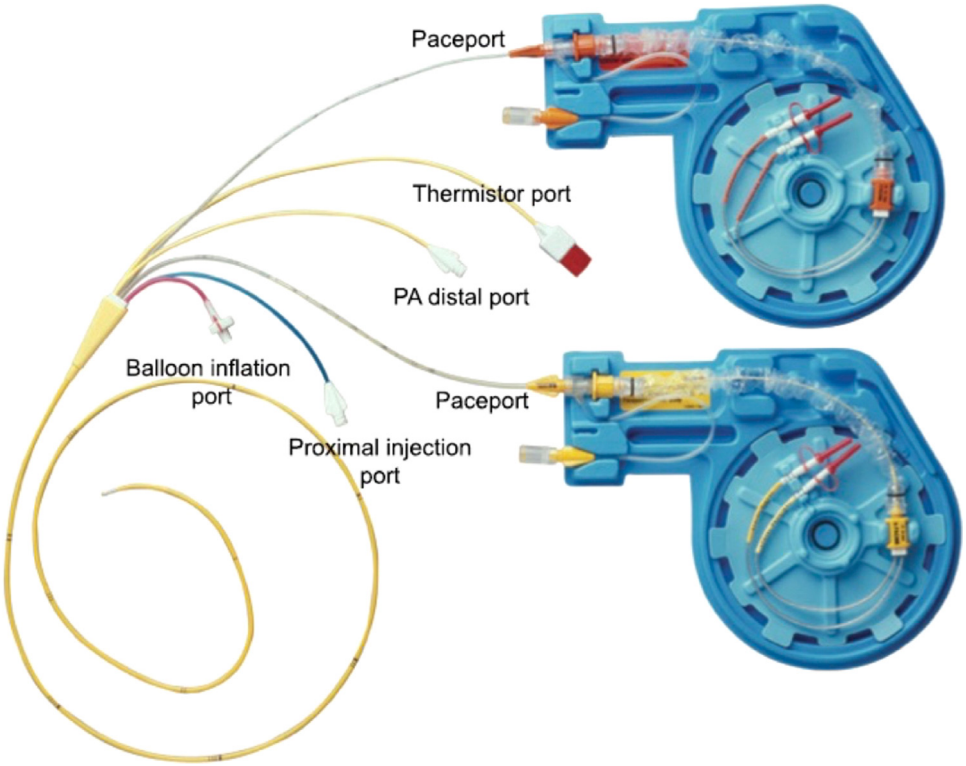

Fig 1. Pulmonary artery catheter with right ventricular port.

either serial transthoracic or transesophageal (TEE) echocardiograms, or ideally continuous monitoring using TEE, are required to evaluate RV health through critical illness and the effects that preload, afterload, and contractility augmentation have on its functionality.

Continuous noninvasive RV monitoring potentially can provide constant insight into the health of the RV and may identify patients in whom the RV is deteriorating before RV systolic dysfunction occurs. One real-time technology that is of particular interest is the disposable, miniaturized TEE that remains in the patient for up to 72 hours without major complications.[16] This would allow the clinical team to observe the effects of interventions to improve the RV preload, contractility, and afterload continuously and in real-time.[16,17] However, the major disadvantage to this technology is that it only provides a monoplane image, with no capability to perform a Doppler (color, spectral) assessment of flow. In addition, there currently is a lack of large-scale data to support its use in ARDS patient populations with RV injury.

Advanced technology PA catheters (Edwards Lifesciences, Irvine, CA) or PA catheters with an RV port (Paceport, Edwards Lifescience, Irvine, CA) enable invasive dynamic assessment of RV function (Fig 1).[18] Real-time invasive monitoring of preload (RV end-diastolic volume index, PA wedge pressure, PA diastolic pressure), contractility (RV ejection fraction, RV stroke work index), and afterload (pulmonary vascular resistance [PVR]) RV indices may detect early RV stress as it occurs, therefore allowing risk stratification and diagnostic and therapeutic decisions to be made earlier in the patient's clinical course.[18]

Although the aforementioned diagnostic approaches make physiologic sense, the assumption that they may confer a benefit and guide appropriate interventions must be confirmed in rigorous and large prospective studies.

Pharmacologic and Nonpharmacologic Therapies

The injured RV is supported best by strategies that optimize myocardial perfusion and reduce RV afterload. The goal is to reduce RV work and halt any adaptation mechanisms that may be occurring in the context of ARDS. Unfortunately, the perfect therapy to achieve these aims does not exist; hence, a combination of therapies often is indicated.

Pharmacologic Therapies

In patients with severe COVID-19, the intense inflammatory response may be associated with significant systemic vasodilatation. The reduction in perfusion pressure, combined with dilatation of the RV, result in reduced myocardial perfusion. Vasopressors, such as norepinephrine and vasopressin, theoretically would improve myocardial perfusion pressure, but they have no role in reducing the PVR and may even increase it.[19-21] Norepinephrine improves RV-PA coupling; however, at high doses, this effect is diminished.[19-21] In very severe vasoplegic states, norepinephrine and vasopressin in combination would act synergistically to improve perfusion pressure. Vasopressin at low doses (0.01-0.03 U/min) may reduce PVR through endothelial nitric oxide release, but this is lost at higher doses from which it also may contribute to coronary vasoconstriction.[19,21]

A commonly preferred combination is an inodilator (milrinone, enoximone, or levosimendan) with a vasopressor, which is intended to ensure positive inotropy is provided while ensuring myocardial perfusion is not compromised.[22] As much as this strategy conforms to the physiologic principles required to support the RV, there are no data or evidence that it confers outcome benefit in this context.[22]

Epinephrine often is described as an inopressor; hence, in the context of RV failure it would provide inotropy and facilitate the preservation of myocardial perfusion. However, this may be compromised by the presence of tachyarrhythmias often associated with its use.[23]

Inhaled pulmonary vasodilators (prostaglandins and nitric oxide) often are used to facilitate a reduction in PVR and reduce RV work, with a consequent increase in RV cardiac output. This effect is appreciated most when patients are in an unstable state attributable to severely impaired RV function; however, it often is not sustained because these drugs exhibit tachyphylaxis, and their use is not associated with an improvement in mortality.[24]

Nonpharmacologic Therapies

In the context of severe acute respiratory failure, the injured RV is likely to benefit from correction of hypoxemia and/or hypercapnia and/or acidemia provided by veno-venous ECMO (VV ECMO) when conventional lung-protective and RV-protective ventilation (low stress and/or strain, low driving pressure, low mechanical power) measures fail.[1,25] The reduction in arterial carbon dioxide and improvement in arterial oxygenation have been shown to be associated with a reduction in the mean pulmonary artery pressures within just 15 minutes of commencing VV ECMO support.[26] However, the presence of RV injury often is not factored into the processes of either the selection or timing of the commencement of ECMO support. There is a notable paucity of rigorous data supporting this practice routinely; however, there is equipoise to investigate this given the burden of RV dysfunction in patients with COVID-19.[5]

COVID-19 is associated with immunothrombosis, myocarditis, and vascular injury, which pose further challenges in managing RV injury in this context despite VV ECMO support (Fig 2). There are reports of patients presenting with significant remixing on VV ECMO due to poor RV ejection, which could be improved only temporarily with inhaled vasodilators.[27] Current evidence suggests that patients requiring mechanical cardiac support (veno-arterial or veno-arterial venous ECMO) have worse outcomes, suggesting that this is a state associated with high mortality.[28]

A different approach would be to provide both respiratory and RV mechanical support. Mustafa et al[29] supported 40 patients with COVID-19 ARDS and pulmonary hypertension, with veno-pulmonary arterial ECMO using percutaneous right

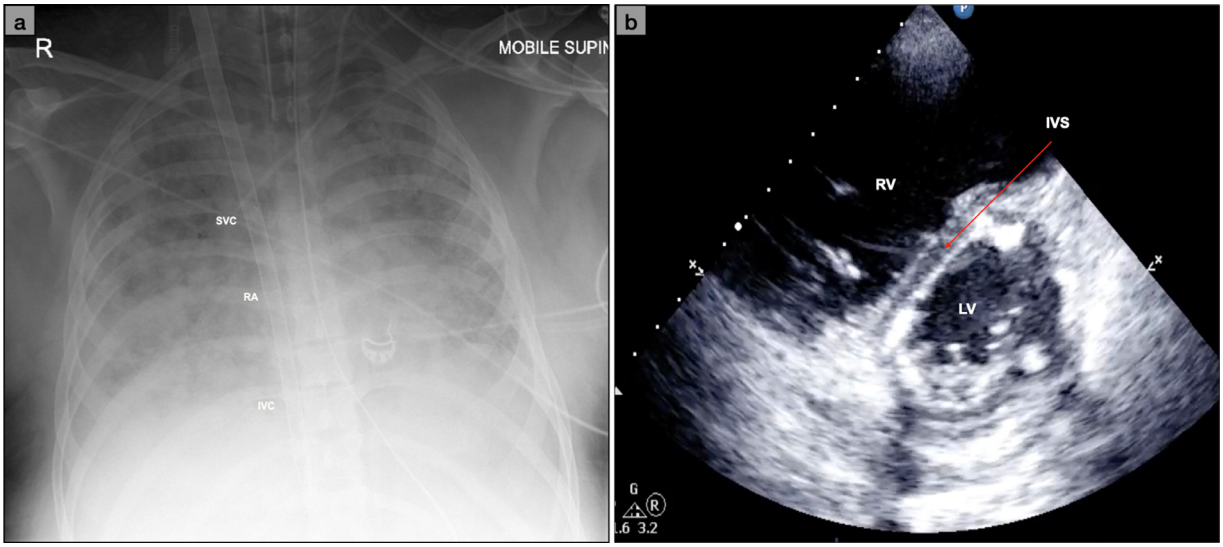

Fig 2. (A) Chest radiograph of a critically ill patient with COVID-19 ARDS receiving VV ECMO support. The image shows a single DLC inserted through the right internal jugular vein with the cannula tip lying in the inferior vena cava. The patient developed refractory RV injury despite VV ECMO support, which led to RV failure. (B) Parasternal short-axis view by transthoracic echocardiography of the same patient a few days after initiation of VV ECMO support. The RV is markedly dilated, pressure and volume overloaded with IVS flattening and characteristic D configuration of the LV despite ongoing effective VV ECMO support. *ARDS*, acute respiratory distress syndrome; *COVID-19*, coronavirus disease 2019; *DLC*, dual-lumen cannula; *ECMO*, extracorporeal membrane oxygenation; *IVC*, inferior vena cava; *IVS*, interventricular septum; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *SVC*, superior vena cava; *VV*, veno-venous.

ventricular assist device. This was provided as part of a bundle of care that included awake ECMO (88% of patients were extubated), early corticosteroids, and optimization of preload.[29] The survival to hospital discharge was 73%, which was considerably higher than most current reports of outcomes of ECMO support in patients with COVID-19 ARDS.[30] In another recent small retrospective analysis, Cain et al[31] found that the early use of a percutaneous right ventricular assist device (at the time of ECMO initiation) may improve mortality in patients with severe COVID-19 ARDS. Mechanistically, these approaches are congruent with the pathophysiologic process associated with COVID-19 (Fig 3). However, there is a need to investigate this further to evaluate if such outcomes are reproducible in prospective trials.

Can We Personalize the Use of Diagnostic Modalities and Therapeutic Interventions?

In the meta-analysis by Paternoster et al,[5] approximately 50% of patients with RV injury did not receive invasive ventilation. This raises the question of RV injury onset and its natural history in spontaneously breathing patients with COVID-19. Does the onset of RV injury correlate with the need for respiratory support? What is the effect of continuous positive airway pressure, noninvasive ventilation, high-flow nasal oxygen, and patient self-inflicted lung injury on the RV? Can these patients be risk-stratified based on the degree of RV injury? These questions should be addressed in future research to timely identify therapeutic targets.

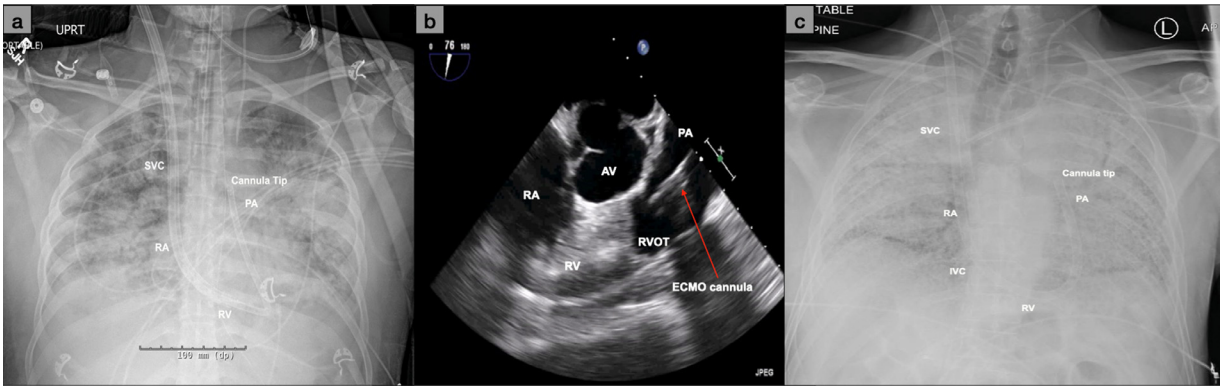

Fig 3. (A) Chest radiograph of a critically ill patient with COVID-19 ARDS receiving V-Pa ECMO support. The image shows a single DLC inserted through the right internal jugular vein with the cannula tip lying in main pulmonary artery (percutaneous RVAD); (B) transesophageal echocardiography of the same patient confirming cannula tip position in the main pulmonary artery; (C) V-Pa ECMO in a patient with non–COVID-19 severe respiratory failure and RV injury. *ARDS*, acute respiratory distress syndrome; *AV*, aortic valve; *COVID-19*, coronavirus disease 2019; *DLC*, dual lumen cannula; *ECMO*, extracorporeal membrane oxygenation; *IVC*, inferior vena cava; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *RVAD*, right ventricular assist device; *RVOT*, right ventricular outflow tract; *SVC*, superior vena cava; *V-Pa*, veno-pulmonary arterial.

Identifying patients at risk and a multimodal assessment of RV biomechanics (eg, a combination of invasive and noninvasive diagnostic modalities) potentially could aid a personalized approach to the management of patients with COVID-19 with respiratory failure and RV injury. Mekontso-Dessap et al[1] developed a clinical risk score for the early identification of ACP in invasively ventilated patients with moderate-to-severe non–COVID-19 ARDS. The score included four variables: (1) pneumonia as cause of ARDS; (2) driving pressure ≥18 cmH_2O; (3) arterial oxygen partial pressure-to-fractional inspired oxygen (PaO_2/F_IO_2) ratio <150 mmHg; and (4) arterial carbon dioxide partial pressure ≥48 mmHg. The prevalence of ACP was 20% and 75% for ACP scores of 2 and 4, respectively.[1] There is merit in validating this clinical score in patient cohorts with COVID-19 ARDS, performing early echocardiography in those at risk of RV injury, and considering invasive RV and PA pressure monitoring in those with a high RV injury score. A combined PAC-based and echocardiography-based RV assessment in ECMO candidates who fail to respond to conventional measures potentially could aid in decision-making regarding ECMO configuration (VV *v* veno-pulmonary arterial).

Conclusions

Right ventricular injury in COVID-19 ARDS increases the risk of death. Severe RV injury remains challenging to manage with conventional lung-protective and RV-protective strategies. Future RV research should focus on mechanisms of RV injury in different disease states leading to ARDS, identification of subclinical RV-PA uncoupling, and RV injury phenotyping. These data will inform further research and subsequently enable evaluation of timely interventions (pharmacologic and mechanical) that potentially could protect the RV and mitigate RV injury and progression to RV failure.

Conflict of Interest

The authors (on behalf of PRORVnet) have received honoraria from Edwards Lifesciences.

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