Commentary: Extreme cardiorespiratory pathophysiology: Critical care evolution in response to a pandemic

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The evolutionary pressure for more efficient gas exchange in highly aerobic vertebrates has given rise to a thin blood–gas barrier that is inherently vulnerable to stress failure, and the separation of the pulmonary and systemic circulations. In the dawn of the COVID-19 pandemic, extracorporeal membrane oxygenation (ECMO) was shown to confer a clear survival benefit in patients with severe respiratory failure compared with maximum ventilator support alone. The acquisition of large clinical data sets has allowed for meaningful interrogation of the incidence as well as influence of right ventricular (RV) dysfunction in extreme respiratory pathophysiology.

Cain and colleagues present data from targeted interrogation of the Outcomes and Recovery after COVID-19/Critical Illness Leading to ECMO (ORACLE) Registry. The ORACLE Registry comprises an interdisciplinary collaboration across 6 academic medical centers focusing on characterization of recovery and survivorship optimization of patients with COVID-19. The authors analyzed retrospectively collected data from 424 patients with COVID-19 undergoing mechanical ventilation of whom 159 were supported with veno-venous ECMO (VV-ECMO). Echocardiograms were performed if clinically indicated with 79.2% of patients undergoing ECMO receiving scans and RV dysfunction being documented in 38.4% of these patients. Apart from increased vasopressor, steroid, and inhaled pulmonary vasodilator use, VV-ECMO support was further associated with increased use of tracheostomy, longer duration of ventilation, and longer hospitalization without significant reduction in mortality. RV dysfunction was found to be significantly associated with increased odds of death in the VV-ECMO cohort (odds ratio [OR], 2.50; 95% CI, 1.17-5.47; \( P = .02 \)).

In a systematic review and meta-analysis including 1861 patients with acute respiratory distress syndrome (ARDS), Sato and colleagues showed an association between the presence of RV injury and increased overall (OR, 1.45; 95% CI, 1.13-1.86; \( P = .003 \); \( I^2 = 0 \% \)) and short-term (OR, 1.48; 95% CI, 1.14-1.93; \( P = .003 \); \( I^2 = 0 \% \)) mortality. The analysis of 9 studies demonstrated that RV injury defined as a spectrum, including RV dysfunction, RV dysfunction with hemodynamic compromise, RV failure, or acute cor pulmonale was present in 21.0% of included patients. Data derived from the Echocardiography Findings in COVID-19 Patients Admitted to Intensive Care Units study illustrated the relationship between RV systolic dysfunction and pressure overload due to positive pressure ventilation, hypercapnia, and pulmonary embolism.

Several groups have shown the association between persistent RV dysfunction whilst receiving VV-ECMO and dismal outcomes. Chotalia and colleagues further identified 3 cardiovascular subphenotypes in relation to RV pathophysiology: normal RV function, RV dilation...
with mostly preserved systolic function, and RV dilation with systolic impairment. Subgroups demonstrated discrepant clinical characteristics and response to prone ventilation and outcomes, with 90-day mortality rates of 22%, 42%, and 73%, respectively \((P < .001)\). In a more recent systematic review and meta-analysis of patients receiving VV-ECMO support as part of management for ARDS, Chad and colleagues\(^\text{10}\) also demonstrated an association between RV injury and mortality \((OR, 2.72; 95\% CI, 1.52-4.85; P < .001; I^2 = 29.8\%)\). The association persisted across 3 subgroups assessing RV dilatation measures \((OR, 3.51; 95\% CI, 1.51-8.14; P < .01), RV function measures \((OR, 1.84; 95\% CI, 0.99-3.42; P = .05)\), and RV measurements post-ECMO initiation \((OR, 1.94; 95\% CI, 1.01-3.72; P < .05)\).

Data from a spatial transcriptomic platform on autopsy-derived lung tissue from histologically confirmed regions of ARDS has demonstrated the unique transcriptional signatures of SARS-CoV-2 and H1N1-induced ARDS.\(^\text{11}\) In contrast to the H1N1 influenza virus profile that was representative of antiviral response, the transcriptional profile of SARS-CoV-2 ARDS is mainly characterized by tissue remodeling pathways. In detail, there was increased expression of epithelial-to-mesenchymal transition, coagulation, and extracellular matrix pathways. This distinctive fibrotic and prothrombotic ARDS phenotype leads to changes at the tissue level that contribute to increased RV afterload and possibly structural changes to the RV myocardium.

The intricacy of RV anatomical architecture is of unparalleled complexity,\(^\text{12}\) with quantitative assessment of RV function remaining challenging to date.\(^\text{13}\) This is further complicated by the fact that transitioning of homeometric to heterometric RV adaptation and eventually RV-pulmonary artery uncoupling remains unpredictable.\(^\text{14}\) In regard to ECMO configuration, veno-pulmonary arterial ECMO,\(^\text{15}\) and veno-arterial ECMO\(^\text{8}\)—both of which provide RV support—have shown encouraging results in selected patients.

The authors’ findings therefore represent more of a collective shared experience.\(^\text{7-9}\) Conducting such a research study during the pandemic required enormous effort and is commendable. Limited knowledge and availability of resources during the breakout of the pandemic, in addition to data collection in the midst not only of evolving SARS-CoV-2 mutations and variants, but also therapeutic paradigms and ECMO acceptance criteria, remain main contributory factors to data heterogeneity and potential confounding. Overseeing any methodological limitations and the obvious causality dilemma, the translational value of these data lie in 2 domains. Firstly, it is apparent that a structured approach to cardiac echocardiographic imaging in the setting of ARDS is required.\(^\text{16}\) Secondly, the necessity of RV-protective ARDS management algorithms providing full cardiorespiratory support whilst lung parenchyma recovery takes place, has become apparent.

**CONCLUSIONS**

All in all, the clinical experience harnessed during the pandemic in extreme cardiorespiratory pathophysiology has been a catalyst for promoting our understanding of mechanical circulatory support in critical care settings. Further grasp of the pathological presentation of different genetic viral variants, variable susceptibilities of human host to infection, and increasingly earlier more precise diagnosis and application of emerging antiviral therapies offers the hope and possibility of improving clinical outcomes. We anticipate the analysis of long-term outcomes of patients enrolled in the ORACLE Registry to appreciate any lasting effects on cardiorespiratory physiology.

**References**


