



## **Pulmonary Vasculopathy in COVID-19 Acute Respiratory Distress Syndrome** A Step Closer to the Full Picture

Since the beginning of the coronavirus disease (COVID-19) pandemic, pulmonary clinicians and researchers have questioned how lung injury from severe COVID-19 fits within our current paradigm of the acute respiratory distress syndrome (ARDS). Authors in the *Journal* have presented data both supporting (1) and opposing (2) the contention that ARDS from COVID-19 is distinct from ARDS due to other etiologies, although in fact COVID-19 ARDS seems just as heterogeneous as ARDS writ-large (3). The pulmonary vasculature has emerged as a key area of interest in severe COVID-19 (4). Pulmonary vascular injury has been observed in non-COVID ARDS for nearly 50 years (5), and contributes to poor outcomes among patients with the syndrome (6). Similarly, pulmonary vasculopathy and endothelial inflammation have featured prominently in many clinical and histopathologic studies of COVID-19 ARDS (7, 8), perhaps in part due to the expression of membrane-bound ACE2 (angiotensin converting enzyme 2) on pulmonary endothelial cells (7). However, the clinical consequences of pulmonary vasculopathy in COVID-19 ARDS remain poorly understood.

In this issue of the *Journal*, Villalba and colleagues (pp. 857–873) combined radiologic, histopathologic, and morphometric analyses to comprehensively characterize pulmonary vasculopathy in COVID-19 ARDS (9). The authors examined 20 consecutive autopsy cases from the Massachusetts General Hospital during the peak of the first COVID-19 wave in the U.S. Northeast (March–May 2020), and compared these COVID-19 lung specimens to samples from 21 historical autopsies of fatal non-COVID ARDS from both viral and nonviral causes. The groups were similar in demographics and therapies received during hospitalization, aside from frequent hydroxychloroquine use among the COVID-19 group—a relic of preclinical and nonrandomized trial data available at that time (10). One-third of COVID-19 decedents were never intubated either because of limitations in invasive treatment as a result of shifting goals of care or death occurring outside the hospital setting; however, they all had clear diffuse alveolar damage (DAD) on lung histopathology and most met or would have met the Berlin ARDS definition. Pre-mortem chest computed tomographic imaging was available for one-third of patients in both groups, with COVID-19 lungs having significantly more dilation of the pulmonary vasculature particularly in dependent lung segments, along with increased mosaic attenuation suggestive of more extensive microvascular obstruction. Evaluation of lung histology using traditional

semiquantitative approaches demonstrated similar findings. DAD was identified in both COVID-19 and non-COVID viral ARDS, yet COVID-19 lungs were more likely to have vascular alterations including capillary congestion and thromboemboli compared with non-COVID ARDS controls.

The authors developed a set of novel morphometric statistics using automated pixel-by-pixel analyses of the pulmonary microvasculature, quantifying the degree of pulmonary vascular congestion (C<sub>vasc</sub>) on lung histology. Regions of cartilaginous bronchi, noncartilaginous bronchioles, and alveolar septae were then manually identified by trained lung histopathologists, allowing the morphometry algorithm to determine C<sub>vasc</sub> separately for all three compartments. Their morphometric analyses yielded multiple insights. First, computer-determined alveolar C<sub>vasc</sub> correlated well with the histopathologists' subjective interpretation of overall vascular congestion, demonstrating the C<sub>vasc</sub> metric's validity compared with traditional histopathology. Overall, alveolar C<sub>vasc</sub> was highest among samples from COVID-19 lungs compared with non-COVID lungs, indicating more substantial pulmonary vascular injury in COVID-19. Additionally, when comparing the most congested regions of each lung, the COVID-19 lungs had higher C<sub>vasc</sub> in all compartments (bronchi, bronchioles, and alveoli) compared with non-viral DAD controls, and higher peri-bronchiolar C<sub>vasc</sub> compared with viral DAD controls. Alveolar and peri-bronchiolar C<sub>vasc</sub> also had wider statistical dispersion in COVID-19 lungs compared with non-COVID DAD, suggesting great heterogeneity in this vascular congestion across the COVID-19-infected lung. Alveolar C<sub>vasc</sub> measurements also correlated with the temporal evolution of DAD, with higher alveolar C<sub>vasc</sub> observed in early phases prior to development of hyaline membranes and with lower alveolar C<sub>vasc</sub> as DAD progressed into the organizing phase. Finally, among all study subjects, alveolar C<sub>vasc</sub> was closely correlated with ventilatory ratio (a clinical surrogate measure for pulmonary dead space fraction) and higher alveolar C<sub>vasc</sub> was associated with worse survival.

Villalba and colleagues have provided an intriguing proof-of-concept study that integrates radiologic, histopathologic, and morphometric phenotyping to provide a novel microarchitectural understanding of pulmonary vasculopathy in COVID-19 ARDS. While this study does not definitively distinguish COVID-19 ARDS from that of other etiologies, it provides compelling evidence that pulmonary vascular injury is an important driver of respiratory impairment and clinical outcomes in fatal ARDS, and such injury is particularly exaggerated in COVID-19. Their work opens new doors for inquiry into the pathologic mechanisms of DAD in general, and demonstrates the strengths of team-based science.

This study has some limitations. As the authors appropriately note, this single-center series captured a limited sample of COVID-19 patients who all died early in the pandemic. Receipt of

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immunomodulatory agents now known to have clinical efficacy in COVID-19 was low, and the authors were not able to identify any difference in pulmonary Cvasc based on receipt of corticosteroids. Furthermore, all COVID-19 cases in this study occurred prior to the emergence of the first SARS-CoV-2 variants of concern (VOCs) (11). While it is quite plausible these findings should apply to later VOCs, assessing if pulmonary vascular congestion differs across variants may help explain observed differences in clinical outcomes across successive waves of the pandemic (12, 13). All samples came from autopsy specimens, so this study does not address if and how these microvascular changes resolve in the post-acute recovery period. As surgical lung biopsies are not commonly performed for severe COVID-19, alternative sampling methods from COVID-19 survivors—such as lung cancer resection specimens—could be considered in future work (14). Lastly, while direct viral infection of pulmonary endothelial cells remains a plausible mechanism for these observations in COVID-19 lungs, further work is needed to characterize the biological drivers of pulmonary microvascular injury and identify potential therapeutic targets (15).

Overall, this study both reinforces what is already known about pulmonary vasculopathy in ARDS while providing fresh data on the spatial and temporal evolution of pulmonary vascular injury during ARDS, as well as its clinical consequences. We look forward to the future clinical and mechanistic insights that this novel work will bring to the ARDS field. ■

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