

## Covid-19, Angiogenesis, and ARDS Endotypes

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The SARS-CoV-2 pandemic has inspired new interest in understanding the fundamental pathology of acute respiratory distress syndrome (ARDS), which has been associated with severe coronavirus disease 2019 (Covid-19). ARDS has long been recognized to be remarkably heterogeneous, with not only a wide range of causes but also a broad spectrum of severity, abnormalities on imaging, and gas-exchange impairment.<sup>1</sup> The form of ARDS that is associated with Covid-19 is no different.<sup>2</sup>

A long-standing goal<sup>3</sup> has been to define endotypes that subdivide ARDS into groups on the basis of distinct biologic and pathologic processes in order to design higher-yield clinical trials and tailor treatment. Ackermann and colleagues now report in the *Journal*<sup>4</sup> their use of novel techniques to better elucidate some of the biologic pathways that result in clinical ARDS. The investigators performed a detailed histologic study of lungs obtained on autopsy from patients with Covid-19 and historical samples from the 2009 H1N1 influenza outbreak (seven samples in each group). Unsurprisingly, both groups had evidence of diffuse alveolar damage, with widespread signs of thrombosis. Such injury to the alveoli is the pathognomonic histologic finding in ARDS, and both microthrombosis and macrothrombosis are also commonly observed.<sup>5</sup> However, Ackermann and colleagues also analyzed the up-regulation of genes associated with inflammatory conditions and unique “intussusceptive angiogenesis” using some new techniques, including immunohistochemical assay, microcomputed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurements of gene expression. The results of these collective methods suggest the presence of increased levels of angiogenesis in human ARDS. The authors further report quantitatively more intussusceptive angiogenesis in the Covid-19 lungs than in the influenza samples and a corresponding differential up-regulation of angiogenesis-associated genes. These findings are intriguing, and it is tempting to ascribe this difference as being specific to SARS-CoV-2. In-

deed, the novelty of the virus has led to a widespread attribution of many findings in patients with Covid-19 to the virus itself.<sup>6</sup>

In the present study, however, several limitations complicate a direct comparison of the Covid-19 and influenza samples. The authors acknowledge that the extent and degree of fibrin organization in the influenza samples, along with a greater weight of the lungs, indicate that these patients had a more advanced stage of diffuse alveolar damage than the patients with Covid-19. Such damage progresses through different stages as time elapses from the initial injury, so this temporal heterogeneity complicates any direct comparison. The authors attempt to control for this confounder by examining the correlation between the degree of angiogenesis and the length of hospital stay, not corrected for the length of illness, variables that they found to be correlated in the Covid-19 group but not in the influenza group. However, since the groups were sampled at different stages of disease, the relevance of this finding is unclear. And there are other important clinical differences between the groups. None of the patients with Covid-19 had been intubated (two had received noninvasive ventilation), whereas the majority of patients with influenza had been intubated and treated with ventilator settings that we would now consider not to be lung protective.<sup>7</sup> The sample size of the study was also small, which is particularly problematic in a heterogeneous condition such as ARDS.

These data are therefore unable to define differences specific to Covid-19 and H1N1 influenza. The investigators' conclusion that “vascular angiogenesis distinguished the pulmonary pathobiology of Covid-19 from that of equally severe influenza virus infection” has to be considered speculative. It should also be noted that regulators of angiogenesis (e.g., angiopoietin-2) have long been acknowledged as ARDS biomarkers,<sup>8</sup> even in the pre-Covid-19 era. Nevertheless, this observation of angiogenesis in an early stage of diffuse alveolar damage is important.

This study emphasizes the heterogeneity that

is fundamental to the clinical syndrome of ARDS, which affects not only prognosis and potential treatment response but also the interpretation of clinical trials.<sup>9</sup> Future studies are needed to determine whether these reported differences in angiogenesis represent distinct time points in a similar disease process or a true endotype that occurs only in a subgroup of patients. Regardless, the finding of a novel pathological process opens up the possibility of developing sorely needed new treatments and should spur further research. In this work, Ackermann and colleagues have made an important contribution that may ultimately lead to a greater understanding of ARDS and perhaps to more precision in the identification of ARDS endotypes.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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