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Microvascular Shunts in COVID-19 Pneumonia

To the Editor:

Throughout the coronavirus disease (COVID-19) pandemic, clinicians and scientists have attempted to understand mechanisms underlying severe hypoxia in individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can be disproportionate to changes in lung mechanics (1). Pathophysiologic mechanisms leading to hypoxia in SARS-CoV-2 are incompletely understood but may include the recruitment of intrapulmonary shunt vessels. Past work has noted the presence of prominent intrapulmonary bronchopulmonary anastomoses (IBA), which represent connections between the pulmonary and bronchial circulations, in severe SARS-CoV-2 (2, 3). Prominent IBA have been previously observed by lung histology and three-dimensional reconstruction from patients dying with SARS-CoV-2, proposing that these vessels contribute to intrapulmonary shunt (2). IBA have previously been identified in several diseases characterized by severe hypoxemia with extensive pulmonary vascular disease, including developmental lung diseases, and in idiopathic pulmonary arterial hypertension (4, 5).

In patients with SARS-CoV-2, Reynolds and colleagues performed studies using contrast-enhanced transcranial Doppler imaging of the bilateral middle cerebral arteries (3). These investigators demonstrated that 83% of the study participants had clear evidence of shunting of agitated saline bubbles into the middle cerebral arteries, which bypassed the pulmonary capillaries (3). Furthermore, the Pa_{O_2}-to-$F_{I_{O_2}}$ ratio was inversely correlated with the number of microbubbles observed (Pearson's $r = -0.55$; $P = 0.02$), suggesting that the larger the shunt, the greater the degree of hypoxemia. With these findings, this group proposed that shunt vessels may further contribute to the pathophysiology and severity of hypoxemia in SARS-CoV-2.

This recent publication by Ackermann and colleagues (6) supports these past observations describing IBA in COVID-19 lungs at autopsy. However, their findings would be further strengthened with more details regarding how vascular types and connections were determined by their extensive imaging methods. The histologic terms that were used, such as describing vessels as "angiomatoid" or "plexiform", are more typically used to describe histologic features of plexiform lesions in severe pulmonary arterial hypertension, observations that were not made in this case series. Both current and past work (7) by this team suggests that neovascularization takes place in severe COVID-19 pneumonia via intussusceptive angiogenesis at capillary levels. This proposal markedly depends on the demonstration of increased numbers of holes within capillary networks from corrosion casts. Production of such tiny and fragile casts is very difficult with highly variable outcomes, and interpretation may be subject to sampling bias. Thorough quantification and cast comparison to other pulmonary disease controls would be helpful. Our view is that the observed microvessels appear dilated and congested and are detectable owing to increased recruitment through enhanced blood flow, which reflects intrapulmonary shunting (2). In fact, alveolar and bronchial capillary abundance due to pathologic congestion is frequently seen in histologic sections of autopsy material in the presence of right heart failure.

Over the years, vascular connections between the pulmonary and bronchial circulations have been given a variety of names, including bronchopulmonary, pulmobronchial, supernumerary vessels, or "Sperrarterien", but their roles during development or in disease have been uncertain. Advances in our understanding of the role of these vessels through comprehensive studies including histology, three-dimensional reconstruction, hemodynamics, and now, advanced imaging provide tools to stimulate future work to better understand their potential contributions to disease. We have proposed the term IBA to describe microvascular pulmonary and bronchial connections that allow for pulmonary arterial blood to bypass alveolar capillaries. Further characterization of mechanisms underlying the developmental basis for and physiologic regulation of IBA may provide insights leading to the development of novel diagnostic and therapeutic strategies to better address the many challenges of severe respiratory failure in patients with SARS-CoV-2, as well as potential roles in "long COVID" during follow-up in survivors. ∎

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Bronchial Mucosal Microcirculation in SARS-CoV-2 Infection: Role in Innate Humoral Defense?

To the Editor:

The circulation furnishing human bronchi with oxygenized blood sems overlooked as regards possible roles in infection diseases. I thus

welcome the advanced images reported by Ackerman and colleagues illustrating peribronchial and perivascular microvessels and showing evidence for excessive bronchiopulmonary shunting by the bronchial circulation in coronavirus disease (COVID-19) pneumonia (1). Arguably, a profuse mucosal microcirculation, supplied by the bronchial circulation, also needs attention in COVID-19.

Cooperation between Mucosal Microcirculation and Overlying Epithelial Barrier

Similar to superficial microcirculations of nasal and tracheal mucosae, but distinct from the pulmonary circulation, responsiveness of human bronchial mucosal microcirculation brings about local plasma exudation at mucosal challenge with toxins, including microbes (2, 3). The involved microvascular–epithelial cooperation may be summarized as follows: Macromolecules extravasate through active formations/closures of endothelial gaps; extravasated bulk plasma moves up between epithelial cells; a minimal hydrostatic pressure increase impacts laterally on epithelial junctions; and without sieving, plasma proteins/peptides traverse the pseudostratified epithelium (2–4).

Thanks to a conspicuous epithelial barrier asymmetry of human airways, plasma proteins/peptides traverse without compromising the normal epithelial defense barrier (2–4). In conducting airways, plasma exudation thus comes forth as a physiological, first-line, innate immune response at mucosal sites of challenge (2–4).

Early Humoral Antimicrobial Defense in Airways with Intact Epithelium

The nonsieved nature of plasma exudation means that coagulation, complement, natural antibody, cathelicidine, etc., molecules have opportunities for joint operations on human intact airway mucosa (2, 4). This power demands control. Thus, plasma exudation restricts to sites of toxin deposition, and its duration is governed by active formation of endothelial gaps that close spontaneously unless challenge is increased (2, 3).

Human nasal inoculation with rhinoviruses and coronavirus 229E causes plasma exudation (determined as fibrinogen in airway surface liquids) that associates with symptoms and lasts until resolution of infection (2, 5).

As respiratory infections proceed down the airways, exudation of plasma proteins from the bronchial microcirculation would be a final outpost mucosal defense. In accord, high amounts of fibrinogen were demonstrated in sputum samples from individuals with asthma infected with influenza AB (6). Indeed, one may ask whether corticosteroid-insensitive plasma exudation has contributed to reduced risk for severe disease observed in cohorts of people with asthma in the current and 2009 (H1N1-influenza) pandemics (2).

Humoral Defense at Epithelial Loss/Regeneration

The exudative nature of asthma is indicated by elevated baseline concentrations of α2-macroglobulin and IgM in bronchial surface liquids (2, 3). Agreeing with epithelial barrier asymmetry, absorption of inhaled molecules has not been increased in asthma (3, 4), nor may it be increased at viral infection (2).