Intrapulmonary Bronchopulmonary Anastomoses in Severe COVID-19–related Acute Respiratory Failure

To the Editor:

The pathomechanism of "silent" severe hypoxemia leading to acute respiratory failure in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is not understood. Dissociation between relatively well-preserved lung mechanics and the severity of hypoxemia has led to the notion that coronavirus disease (COVID-19)-related respiratory failure is an atypical form of acute respiratory distress syndrome caused by a possible loss of vasoregulation affecting the distribution of blood flow in a compliant lung (1). This failed vasoregulation was associated with a severe intrapulmonary shunt, as assessed by the number of microbubbles via transcranial Doppler after injection of agitated saline in a central or peripheral venous catheter (2). The presence of low Pa_{O_2}/FI_{O_2} ratios was found to be strongly linked to large numbers of microbubbles, suggesting marked intrapulmonary shunt physiology (2). A recent study using dual-energy computed tomography in a cohort of 35 patients with COVID-19 found perfusion disturbances characterized by coexistence of intrapulmonary shunts, dead space, and high and low gas/blood ratios (3).

Although the knowledge of COVID-19 lung histopathology and the underlying disease mechanism has grown over time because of an increased number of autopsy studies, the microscopic basis of COVID-19–related profound hypoxemia has yet to be fully elucidated. Recent studies using three-dimensional (3D) histologic imaging (4) and hierarchical phase-contrast tomography have emphasized the role of bronchial circulation in COVID-19 pneumonia (5) and suggested a right-to-left shunt potentially resulting from the recruitment of intrapulmonary bronchopulmonary anastomoses (IBAs) (4). IBAs bypass alveolar capillary beds by using the bronchial circulation to direct blood from pulmonary arteries (PAs) to pulmonary veins. These unique precapillary anastomoses may create a right-to-left vascular shunt, which has been described in a wide variety of developmental lung disorders and pulmonary hypertension (PH), including, among others, alveolar capillary dysplasia (6) and bronchopulmonary dysplasia (7). Synchrotron-based imaging combined with 3D image reconstruction provides submicrometer resolution to trace precapillary lung vessels precisely and has recently been used to confirm the presence of IBAs in alveolar capillary dysplasia (8) and PH-associated plexiform lesions (9, 10).

Here we report a case of a 17-year-old girl who died of COVID-19–related respiratory failure shortly after an acute onset of shortness of breath and chest pain. We aimed to confirm IBA recruitment in COVID-19 respiratory failure using a combination of histology and synchrotron-based imaging methods. The patient was a 17-year-old girl with obesity who experienced a 1-week prodrome of upper respiratory symptoms, fever, and nausea/emesis and presented with acute shortness of breath and chest pain. She was intubated shortly after admission because of increasing hypoxia. Computed tomography of the chest demonstrated extensive bilateral diffuse patchy pulmonary opacities without cavitation, small bilateral pleural effusions, and mild cardiomegaly but no evidence of pulmonary embolus. Although technically difficult because of the patient's obesity, serial echocardiograms did not show evidence of PH or cardiac dysfunction. Her serum N-terminal probrain natriuretic peptide was elevated at 214 pg/ml. Her white blood cell count and differential were normal. She had a positive test result for SARS-CoV-2, and there was a clinical concern for hyperinflammation. Management included intubation with prone positioning and treatment with remdesivir, steroids, antibiotics, tocilizumab, and anakinra. Despite these measures, her condition progressed to acute respiratory distress syndrome and pressor-refractory hypotension, and she died 2 weeks after presentation. Autopsy studies included cannulation of the main pulmonary vessels and injection of the main PA with blue ink and the main pulmonary veins with orange ink. Extensive tissue sampling (20 lung tissue blocks) for histologic studies in addition to synchrotron-based phase-contrast imaging, followed by 3D image reconstruction, were performed. At autopsy, the lungs were consolidated and heavy. Evolving hyaline membrane disease, extensive acute and focal organizing PA thrombi, and bronchiolar fibrin casts/plugs dominated the histology. Patchy hemorrhagic necrosis and focal necrotizing vasculitis were also noted. Widely open IBAs were revealed by histology via ink injection (Figure 1) and synchrotron imaging (Figure 2); both showed open anastomotic connections between the PA and the bronchial vasculature.

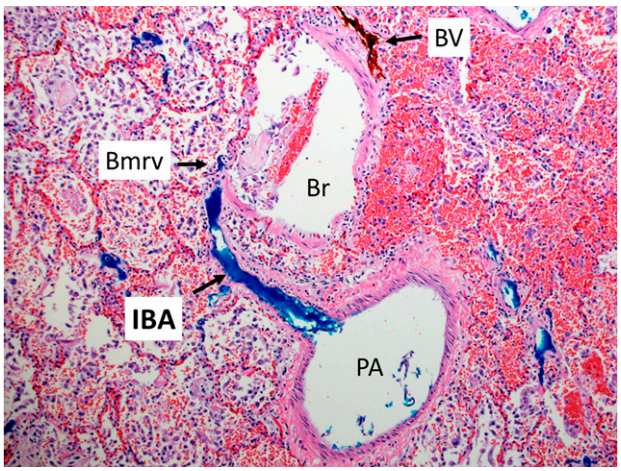

Figure 1. Histological section (original magnification, 10×; hematoxylin-eosin stain) shows a widely open intrapulmonary bronchopulmonary anastomosis (IBA) that connects a pulmonary artery (PA; injected with blue ink) to bronchial microvessels (Brmv), which surround a bronchiole (Br). Brmv contain blue ink, confirming continuity with PA. A dilated bronchial vein (BV) is also shown (double arrow; injected with orange ink). Ink injection was performed as previously described (6, 8, 9).

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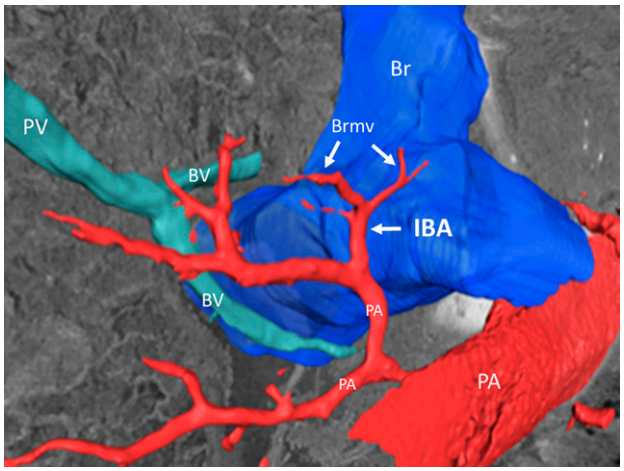

Figure 2. Synchrotron imaging of approximately the same anatomic area as in Figure 1. Three-dimensional (3D) imaging reconstruction highlights intrapulmonary bronchopulmonary anastomosis (IBA) connections between pulmonary artery (PA) and bronchial microvessel (Brmv). PA, red; bronchiole (Br), dark blue; pulmonary vein (PV), light blue; bronchial vein (BV), light blue. Synchrotron imaging and 3D image reconstruction were performed as previously described (8, 9).

The identification of histopathologic correlates is necessary to better understand the pathomechanism of COVID-19–related severe respiratory failure. In this study, we confirmed the presence of recruited IBA with multiple methodologies. We speculate that hypoxia-induced systemic (bronchial) vasodilation in the distal lung may be a trigger for increased intrapulmonary shunt with IBA recruitment, as has been suggested previously (11). We propose that IBAs play a key role in COVID-19 respiratory failure by inducing precapillary right-to-left vascular shunts that contribute to severe and often intractable hypoxemia and death. Additional pathology, including diffuse alveolar damage, airway obstruction, and endothelial cell damage, likely contributed to the overall hypoxic respiratory failure. Although right-to-left intrapulmonary shunt is the most likely explanation, measuring shunt directionality was not possible in this study. Local factors in the distal lung, including inflammation, endothelial dysfunction, local differences between PA and systemic (bronchial arterial) vasomotor regulation, and pressure differences and other factors, likely play a role. We further propose that altered IBA and bronchial vascular function should be emphasized when modeling pulmonary and systemic vascular pathology in severe COVID-19 respiratory failure (12). ■

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