Early View

Research letter

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Intrapulmonary Bronchopulmonary Anastomoses in COVID-19 Respiratory Failure

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To the Editor:

The spread of severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) has led to a devastating and world-wide pandemic disease known as the coronavirus disease (COVID-19). COVID-19 causes acute hypoxic respiratory failure (COVID-ARF), a major cause of mortality and morbidity, with an incompletely understood pathophysiologic mechanism. Gattinoni and colleagues noted that patients with COVID-ARF patients have lung disease that is often characterized by a remarkable dissociation between relatively well-preserved lung mechanics, including lung compliance, and severe hypoxemia. These findings are consistent with the concept that profound hypoxemia occurring in ventilated patients with highly compliant lungs could be due to the loss of regulation of lung perfusion and impaired hypoxic pulmonary vasoconstriction. Early autopsy studies suggest that the lung circulation is a major target of coronavirus infection, which leads to striking pulmonary vascular disease due to variable degrees of thrombosis, apoptosis, edema, inflammation and angiogenesis. These changes contribute to dysregulation of the pulmonary vasculature, which induces perfusion abnormalities and contributes to the physiological phenotypes reported in COVID-19 pneumonia. Further, computerized tomography suggests a unique “tree in bud” appearance of small pulmonary arteries and transcranial agitated saline microbubble doppler studies of COVID-19 patients with hypoxemia have demonstrated intrapulmonary shunting of these bubbles, and that the presence and degree of transpulmonary bubble transit correlates with the degree of hypoxemia. Despite these studies, histopathologic correlates of severe hypoxemia and shunt in the setting of relatively normal lung compliance in COVID-19 patients are largely lacking.
The presence of prominent intrapulmonary bronchopulmonary anastomoses (IBA) connecting pulmonary arteries (PA) and bronchial arteries (BA) bypassing alveoli have been characterized by 3-dimensional (3-D) reconstruction of tissue sections and identified as a potential source of right-to-left shunt with profound hypoxemia in several disorders of the lungs including idiopathic pulmonary hypertension (PH) and chronic thromboembolic PH. IBA represent pre-existing vascular connections between the bronchial and pulmonary vascular trees that are normally prominent during fetal life, appear to close at birth but can be present afterwards, especially with disease. The physiologic roles of these shunt vessels are incompletely understood but appear to contribute to hypoxemia due to right-to-left shunt in response to exercise, hypoxia, and catecholamine challenge. These precapillary anastomotic connections with a diameter ranging from 15-500μm have a capability to redirect deoxygenated blood to bypass the pulmonary microvascular bed leading to poor perfusion of the distal lung. Whether these vascular connections are prominent in COVID-19 lungs, reflecting recruitment of shunt vessels, has not been investigated. We hypothesized that IBA are recruited in lungs of patients who died of COVID-19 with acute respiratory failure with profound hypoxemia.

The study was approved by the Institutional Review Board of Icahn School of Medicine at Mount Sinai. We collected archived autopsy lung tissues from three COVID-19 patients. Hematoxylin-eosin (HE) stained slides of two tissue blocks of each patient’s lung were reviewed. Routine HE sections in combination with trichrome stain and immunohistochemical stains (CD31, smooth muscle actin stains) were used to define the lung architecture and microanatomy. Our study focused on vessels in the distal lung, the sites of gas exchange, so the vessels studied were neighboring terminal and respiratory bronchioles (with a range of airway diameter of 250-
600 microns) and in the distal airspace. The structures and pathways of IBA were further studied with photographs from serial sections to create a Z-stack and then three-dimensionally (3D) reconstructed using Free-D computer software program.\(^\text{19}\)

The demographics of the selected patients reflect a typical COVID-19 patient population with age range at the time of death of 69-86 years, male to female ratio of 2:1, common associated comorbid conditions of hypertension, diabetes mellitus, chronic kidney disease, and short hypoxemic disease course after COVID-19 positive test (2-10 days). All patients received COVID-19 related medication including azithromycin and hydroxychloroquine. Chest X-rays showed patchy opacities in all patients.

Histopathologic examination coupled with 3D reconstruction revealed the presence of prominent IBA in all 3 patients. The profiles of IBA revealed widely open anastomotic vascular connections between pulmonary and bronchial vasculature, confirmed through 3D reconstruction (Figure 1). Dilated bronchial microvasculature and IBA with sizes up to 75μm in diameter were identified in all patients. We did not find histologic evidence of endotheliitis, capillary microthrombi, or arterio-venous malformation. One patient had a thrombus within a distal pulmonary vein. Two patients had emphysematous changes. Histopathologic changes related to acute lung injury were seen in all samples including the variable combination of viral pneumonia, airway and interstitial inflammation, edema, and hyalin membrane disease.

Although the exact pathophysiologic mechanisms underlying severe hypoxemia in subjects with COVID-19 are uncertain, recent clinical, imaging and autopsy studies have identified abnormal
pulmonary vasculature\textsuperscript{2-4} with intrapulmonary right-to-left shunt\textsuperscript{5} as key players in the development of silent but profound and unresponsive hypoxemia, which leads to the significant morbidity and mortality in COVID-19 patient population. Our findings are not only in concert with the pulmonary vasculopathy paradigm developed from recent imaging studies,\textsuperscript{3,5} but it further suggests that prominent IBA may be the microanatomical correlates of COVID-19-related hypoxemia. Using rigorous histologic assessment combined with computerized 3D image reconstruction, we identified prominent and recruited IBA and suggest these are potential histologic correlates of intrapulmonary right-to-left shunt. Pulmonary thrombosis has been a common finding in COVID-19 patients.\textsuperscript{2-4} Although we did not find microthrombi, we did identify a thrombosed pulmonary vein in one patient. Bronchial vessel connection to pulmonary vessels along with abnormal pulmonary veins have been described in adult patients with chronic thromboembolic pulmonary hypertension suggesting a link between thrombotic events and the recruitment of IBA in COVID-19 patients.\textsuperscript{13} Inflammatory and infectious airways disease has been shown to induce recruitment of IBA and it is possible that IBA are present in patients with COVID-19 respiratory failure and hypoxemia.\textsuperscript{20,21}

We propose that the recruitment of IBAs and the dilated bronchial microvasculature are potential sites through which deoxygenated blood travels from right-to-left, bypassing the alveolar capillary network and impairing gas exchange (Figure 1). Our findings support the recent agitated saline ultrasound study that suggests intrapulmonary right-to-left shunts as a pathologic explanation for the profound hypoxemia in COVID-19 patients.\textsuperscript{5} This initial hypoxemia with obstruction and poor perfusion of the distal capillary bed may be worsened by IBA recruitment, which gives rise to a profound right-to-left shunting of blood. This shunt
further reduces distal lung perfusion and compromises gas exchange, leading to intractable hypoxemia and death. Focused studies on the regulation of IBA may lead to unique strategies that can attenuate the morbidity and mortality of patients who contracted SARS-CoV-2.

References:


Figure legend

Figure 1. The combination of serial HE sections, and 3D image reconstruction identifies recruited intrapulmonary bronchopulmonary anastomoses (IBA) in COVID-19 patients. Panel A shows 3 representative images from the 30 serial HE sections analyzed. Z-stack of HE sections showing an area of broncho-arterial bundle was first created (panel B left, virtual light brown sections represent the approximate areas of the numbered HE sections in the Z stack) and a 3D image with oblique representation was reconstructed (panel B right). There is a wide open IBA (brown in 3D image, small arrow in HE-section 19) that connects the pulmonary artery (PA, blue) with the bronchial artery (BA, yellow). (Bronchiole is green and endothelium of BA, IBA, and PA is highlighted by red color). Cartoon (Panel C) demonstrates the microanatomy of intrapulmonary right-to-left shunt Pulmonary blood flow in the distal lung at the terminal bronchiolar level is rearranged in COVID-19 patients. In the normal lung (left panel), the deoxygenated blood (blue arrow) in the pulmonary arteries (PA) enters the alveolar capillary bed (AC) for gas exchange, and the oxygenated blood (red arrows) is collected via pulmonary veins (PV) and enters the left heart. Small amount of oxygenated blood (red dashed arrow) supplies the terminal bronchiole (green color) via the bronchial artery (BA) and the bronchiolar
capillary network (BC). The deoxygenated blood (dashed blue arrow) is collected by bronchial vein (BV) and consequently the pulmonary vein that enters the left heart. The intrapulmonary bronchopulmonary anastomoses (IBA, brown color) are closed and no blood flow between pulmonary and bronchial vascular trees is present. In the COVID-19 lung (right panel), the majority of deoxygenated blood in the distal pulmonary arteries does not reach the alveolar capillary network for gas exchange (dashed blue arrow), but is redirected (blue arrows) through open intrapulmonary bronchopulmonary anastomoses towards the bronchial arteries and bronchial microcirculation bypassing the alveolar capillary bed. The bronchial arteries, capillaries and veins are passively dilated due to the massive amount of blood coming from the right heart. The blood remains deoxygenated and is collected by the bronchial veins and enters the left heart via pulmonary veins contributing to the profound systemic hypoxemia experienced by COVID-19 patients.