However, epithelial shedding characterizes asthmatic bronchi. Hence, the unchanged absorption penetrability remains puzzling. Or is plasma exudation the answer?

In vivo data, obtained in experimental test systems with close structural and physiological similarities to human airways (3, 4), suggest that airway mucosal microcirculations promptly contribute barrier functions at sites of epithelial loss: Patchy, asthma-like denudation (no bleeding or basement membrane injury) promptly induces plasma exudation that creates and sustains a fibrin–fibronectin gel restricted to the site of epithelial loss. Under the biologically active, defense- and repair-promoting barrier gel, all types of neighboring epithelial cells promptly dedifferentiate into rapidly migrating, tethered repair cells. As soon as a new cellular barrier of interdigitating repair epithelium is established, plasma exudation stops, and the gel is shed. Hence, tiny patches of epithelial loss, as would occur in asthma and at viral infection, may not necessarily cause major barrier breaks (2, 4).

Whereas Ackerman and colleagues (1) highlight bronchial circulation remodeling in advanced COVID-19, this letter concerns physiology of bronchial mucosal microcirculation at early stages of respiratory viral infections. As discussed elsewhere (2–4), the present humoral defense aspects have gone under the radar and not yet been addressed in COVID-19 studies. In summary, exudation of proteins/peptides from bronchial mucosal microcirculation warrants attention in studies of factors that reduce progress of airway infections toward alveolar and pulmonary circulation injury and beyond. ■

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Reply to Bush *et al.* and to Persson

From the Authors:

We are grateful for the interest by Bush and colleagues and Persson in the role of the bronchial circulation in the pathophysiology of coronavirus disease (COVID-19). Using synchrotron radiation-based hierarchical phase-contrast tomography (HiP-CT), microvascular corrosion casting, and conventional light microscopy (1), our data demonstrated the recruitment and expansion of peribronchial and perivascular arteriovenous anastomoses in COVID-19. Combined with our earlier work showing that the pulmonary pathophysiology of COVID-19 is characterized by the involvement of endothelialitis, microthrombi, and intussusceptive angiogenesis, these data have altered the perception of COVID-19 from a respiratory illness to a microvascular disease (2). Bush and colleagues and Persson remind us of additional practical considerations in the study of COVID-19.

In our recent work, we have gained new three-dimensional insights into the pulmonary and bronchial circulation in whole lung lobes. These studies were performed using synchrotron radiation-based HiP-CT (3) at the European Synchrotron Radiation Facility. In contrast to the reconstruction of histological serial sections, HiP-CT can bridge tissue structure with high-resolution morphologic detail-revealing structure from the major airways down to the finest microvasculature in an intact lung.

The existence of arteriovenous anastomoses (4, 5) and "Sperrarterien" (5) between pulmonary and bronchial circulation was studied intensively by anatomists in the middle of the last century by histological serial sections and corrosion casting. These specialized arteries are essential in the regulation of intrapulmonary arteriovenous shunting. The Sperrarterien are located in the subpleural tissue, mainly at the septal margin of secondary pulmonary lobules as well as on the mediastinal pulmonary surface (5, 6). Although the pulmonary circulation accounts for 97% of total circulation in the lung and the bronchial circulation for 3% under physiological conditions, there is growing evidence that the bronchial circulation can dramatically increase as a result of arteriovenous shunting and a triggered perfusion of Sperrarterien. The increase in bronchial perfusion may play a pivotal role in a variety of clinical lung problems, such as pulmonary embolism, neoplasms, chronic inflammation and

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COVID-19 pneumonia, by maintaining lung perfusion despite pulmonary arterial insufficiency.

The microvascular adaptations of these bronchopulmonary interconnections by an expansion of this vascular plexus are consistent with the observation of compensatory angiogenesis by intussusception. Intussusceptive angiogenesis is a dynamic morphogenetic process capable of adapting the architecture of the microcirculation to hemodynamic changes, inflammatory injury, and metabolic demands (7, 8). This rapidly adaptive process may involve endothelial progenitor cells, circulating angiogenic cells, or monocytes (7). The presence of intussusceptive angiogenesis is evidenced by numerous transcapillary intraluminal pillars with a diameter of 2–5 μm and has been observed by different imaging techniques in many organs of patients with COVID-19 (e.g., lung, heart, or placenta [8–10]), reflecting the adaptive vascular repair mechanisms to SARS-CoV2–induced injury.

Vascular change may reflect other processes as well. The formation of complex vascular formations such as plexiform or glomeroid lesions are morphological hallmarks of severe pulmonary hypertension. Our group has demonstrated the three-dimensional vascular remodeling of plexiform lesions in idiopathic pulmonary hypertension (11) and chronic thromboembolic hypertension (12). The expansion of plexiform lesions by intussusceptive angiogenesis can result in collateral circulation between the pulmonary and bronchial vessels—presumably an adaptive response to overcome the hypoxia and compromised perfusion (12). In our study on the bronchial circulation in COVID-19 pneumonia, microvascular corrosion casting and HiP-CT could show the evidence of plexiform- and angiomatoid-like lesions at the septal margins to a lesser extent than with severe pulmonary hypertension. These results highlight the transient compensatory effects of microvascular shunting and angiogenesis on the SARS-CoV-2–associated thrombotic microangiopathy. Further investigations should be conducted to elucidate the involvement of the bronchial circulation in the varied clinical presentation of patients with COVID-19. ■

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Erratum: Reconsidering the Utility of Race-Specific Lung Function Prediction Equations

The article by Baugh and colleagues (1), published in the April 1, 2022, issue of the *Journal*, contains an error in the author line. The name of one of the coauthors, Dr. Igor Barjaktarevic, was inadvertently misspelled as "Igor Barjakteravic." For the convenience of our readers, the *Journal* is replacing the online version of the article with a corrected version. ■

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