cryobiopsy technique (15) before treatment and 3 months after treatment. The hematoxylin and eosin– and periodic acid–Schiff–stained slides were evaluated by a pathologist and graded. The example provided in the manuscript is visually very compelling, with a remarkable reduction in goblet cell density and the amount of mucin staining. There was a reduction in the goblet cell hyperplasia score from 1.48 (SE, 0.91) at baseline to 0.91 (SE, 0.81) after treatment. There are some caveats that hamper such histological studies, including the following: the biopsy process itself may affect subsequent findings because of the scarring and healing effect of the biopsy; sampling errors are possible; the scoring process is not validated; the scoring is done with a qualitative approach; and the scoring was performed by a single pathologist. Nevertheless, this key piece of evidence supports the concept of epithelial resurfacing correcting some of the abnormalities observed in chronic bronchitis, and the approach merits further evaluation. ■

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

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Computed Tomography Vascular Tree-in-Bud: A Novel Prognostic Imaging Biomarker in COVID-19?

As of July 14, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease (COVID-19), has infected more than 13 million and killed nearly 600,000 individuals worldwide (1). The predominant mode of morbidity and mortality in COVID-19 is respiratory failure related to acute lung injury and hypoxia (2, 3). Although the histopathological features in the airways and parenchyma of COVID-19 lungs are largely indistinguishable from those of other viral pneumonias, including influenza, there is mounting evidence to suggest that SARS-CoV-2 infection causes significant vascular damage, leading to pulmonary angiopathy (2, 4, 5). Consistent with this notion, many patients present to medical attention with hypoxemia that is out of proportion to the severity of patient symptoms, leading in some cases to "silent hypoxia." Though

R.L.E. is supported by Natural Sciences and Engineering Research Council (NSERC) of Canada postdoctoral fellowship. D.D.S. is supported by a Tier 1 Canada Research Chair and the de Lazzari Family Chair at HLI.

Originally Published in Press as DOI: 10.1164/rccm.202007-2833ED on July 20, 2020

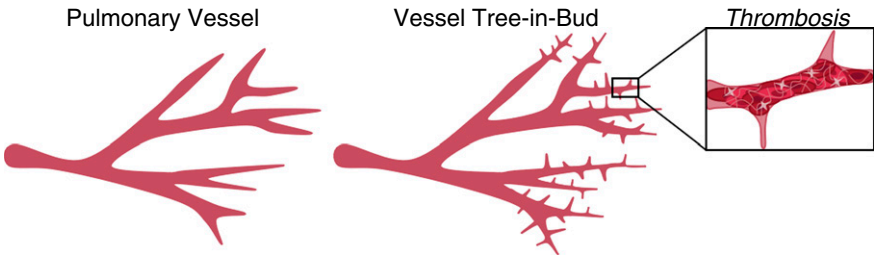

Figure 1. Computed tomography (CT) vessel tree-in-bud schematic in coronavirus disease (COVID-19). Compared with normal pulmonary vessels (left), peripheral vessels in COVID-19 (middle) are resolved on CT imaging and demonstrate a tree-in-bud pattern. Hypercoagulability and lack of fibrinolysis in COVID-19 driving pulmonary thrombosis likely enhances the peripheral pulmonary vessels on CT imaging to cause the tree-in-bud pattern, although the direct pathologic cause is not yet determined.

the exact pathophysiological mechanisms for severe COVID-19 pneumonia are not fully known, provocatively, select autopsy series have shown diffuse thrombosis in the pulmonary microvasculature (4, 5). A deeper understanding of the underlying pathophysiology of COVID-19 and simple *in vivo* biomarkers are crucially needed to predict disease prognosis and to implement targeted precision therapy in these patients.

Computed tomography (CT) imaging of the chest has played a large role in the management of patients with COVID-19. However, to date, the literature has primarily focused on parenchymal abnormalities such as ground-glass opacities (6). In this issue of the *Journal*, Patel and colleagues (pp. 690–699) (7) evaluated pulmonary vasculature on CT imaging and its physiologic and hematologic correlates in mechanically ventilated patients with severe COVID-19 pneumonia. This retrospective study included 39 consecutive patients with acute COVID-19 respiratory failure who showed increased physiologic dead space as evidenced by reduced dynamic compliance (mean, 33.7 ml/cm H_2O) and elevated ventilatory ratio (mean, 2.6), in agreement with previous results (8) and suggestive of marked vascular involvement. Pulmonary vascular abnormalities were assessed by the presence of dilated peripheral vessels, identified as a vascular "tree-in-bud" pattern, as well as pulmonary perfusion abnormalities in a subset of 18 patients who were able to undergo dual-energy CT imaging. Vascular tree-in-bud was evident in 64% of the patients, who had at least two assessable lung lobes (i.e., without dense parenchymal opacification), whereas perfusion defects were present in all 18 patients who underwent dual-energy CT imaging. Additional laboratory investigations and thromboelastography indicated a state of hypercoaguability with reduced fibrinolysis specific to the pulmonary vasculature as a possible mechanism underlying the CT pulmonary vessel and perfusion abnormalities in these patients. Dilated pulmonary vessels (9, 10) and perfusion abnormalities (11) have previously been noted in case reports and larger studies of COVID-19, and this work extends these findings with clinical correlates of pulmonary thrombosis.

The identification of pulmonary vascular tree-in-bud in COVID-19 is unique and interesting. CT tree-in-bud is most commonly reported in peripheral airways disease related to an infectious etiology (12), whereas the vascular manifestation has only been reported in the context of pulmonary tumor thrombosis (12, 13). Here, Patel and colleagues (7) showed an association between the presence of the vascular tree-in-bud pattern (yes vs. no) and duration of ventilation and hospitalization at the time of CT imaging, with a majority of patients who demonstrated vascular tree-in-bud on CT imaging experiencing 10 or more days of ventilation and hospitalization (both $P = 0.01$). These findings are intriguing, and it is tempting to speculate that the vascular tree-in-bud on CT imaging may be a prognostic biomarker for worse outcomes in COVID-19. Indeed, given the small sample size of this study, it may even be an exquisitely sensitive imaging biomarker. However, the posthospital outcomes in these patients were not stated in this study, and as such, it remains to be established whether vascular tree-in-bud is related to mortality in severe COVID-19.

A major limitation of this work is the lack of histopathological correlates of the *in vivo* CT findings. Autopsy of COVID-19 lungs strikingly shows diffuse microthromboses (4, 5), which is consistent with the idea that vascular tree-in-bud in COVID-19 represents an imaging phenotype of pulmonary thrombotic angiopathy, but direct comparison with histopathological specimens is required to confirm whether these are indeed thrombotic events. Future work relating postmortem histopathology to CT imaging acquired during hospitalization, even retrospectively, will allow for identification of *in vivo* factors and biomarkers that are predictive of mortality and can be used to target those patients who have the greatest risk for poor outcomes for appropriate treatment.

Many aspects of the pathophysiology and treatment of COVID-19 are still unclear (14). In this work, Patel and colleagues (7) have made an important contribution to the evolving understanding of pulmonary angiopathy in COVID-19. Whereas CT ground-glass opacities are common in COVID-19 but nonspecific, vascular tree-in-bud is a unique CT finding that may be indicative of poor prognosis in mechanically ventilated patients with severe COVID-19. Figure 1 provides a schematic of the pulmonary angiopathy that likely drives CT vascular tree-in-bud in COVID-19 based on the current study (7): pulmonary thrombosis caused by hypercoaguability and lack of fibrinolysis that enhances the peripheral pulmonary vessels on CT imaging. If the true cause of vascular tree-in-bud is determined, there is budding opportunity for vascular tree-in-bud as an *in vivo*, noninvasive biomarker of COVID-19 for prognosis, to enrich clinical trials for targeted therapy, and to evaluate treatment response and $n = 1$ precision treatment. ■

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

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Use of Hydrocortisone Based on Plasma Biomarkers in Patients with Septic Shock: Another One Bites the Dust?

In 2018, the ADRENAL (Adjunctive Glucocorticoid Therapy in Patients with Septic Shock) and the APROCCHSS (Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock) trials were published (1, 2). Both trials compared the use of hydrocortisone versus placebo in adults with septic shock and found that hydrocortisone reduced time on mechanical ventilation, time to resolution of shock, and time in the ICU. Although the APROCCHSS trial showed a reduction in mortality with hydrocortisone use, this was not confirmed in the ADRENAL trial. Data from APROCCHSS and ADRENAL were subsequently included in updated systematic reviews and meta-analyses, which confirmed the findings from the two large trials (3, 4). Based on this, an international clinical practice guideline proposed a weak recommendation in favor of corticosteroids in patients with sepsis, including septic shock (5). Although most clinicians—based on the results of the trials and systematic reviews and on the proposed weak recommendation in the clinical practice guideline—may consider using hydrocortisone in patients with septic shock, especially in those with refractory shock, there is more uncertainty about the value of treatment with hydrocortisone based on plasma biomarker levels.

In this issue of the *Journal*, Cohen and colleagues (pp. 700–707) report the results of a cohort study nested within the ADRENAL trial (6). The authors assessed whether prerandomization baseline levels of the plasma biomarkers cortisol, aldosterone, and

Supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011) (M.S.-H.). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health and Social Care.

Originally Published in Press as DOI: 10.1164/rccm.202005-1984ED on June 10, 2020