



Early View

Correspondence

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Reply to:

Intrapulmonary Shunt and Alveolar Dead Space in a Cohort of Patients with Acute COVID-19 Pneumonitis and Early Recovery

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To the Editors,

with the greatest interest, we have recently read the paper by Harbut and colleagues describing the role of intrapulmonary shunting and alveolar dead space in patients with acute COVID-19 pneumonitis (1). We are grateful for them sharing their valuable functional blood and alveolar gas exchange data, pointing out a significant alveolar dead space of nearly 30 percent in COVID-19 recovered patients, suggesting a persistent pulmonary vascular pathology. Although the COVID-19 related hypoxemia is characterized by preserved oxygen saturation, a ventilation-perfusion mismatch and increased alveolar ventilation/perfusion ratio (V'_A/Q') heterogeneity, the underlying morphological evidence of this physiological enigma has not been fully understood.

In a recent study (2), we could demonstrate the involvement of the secondary pulmonary lobules in the fatal trajectory of COVID-19 using ultra-high resolution synchrotron radiation based hierarchical phase-contrast tomography (HiP-CT) (3) (Figure a-c). We observed a distinct, mosaic-like consolidation of individual secondary pulmonary lobules based on microvascular occlusion and secondary lobular microischemia, reflecting the increased alveolar dead space described by Harbut *et al.* (1). Moreover, this septal microischemia was accompanied by a periseptal thickening (F) and pronounced dilatation and expansion of the bronchial circulation plexus by opening of intrapulmonary bronchopulmonary shunts and "Sperrarterien" (specialized blockade arteries of the bronchial circulation) (4,5) and an excessive blood vessel neof ormation by intussusceptive angiogenesis, especially in the interlobular septae (2,6,7) (Figure d-g). Intussusceptive angiogenesis is a highly dynamic morphogenetic process involving circulating angiogenic cells, endothelial progenitor cells or monocytes (6), observed in numerous organs of fatal COVID-19 cases (lung, heart, brain, or placenta) as well as in e.g. fibrosing interstitial lung diseases and malignant neoplasms.

We hypothesize that, reminiscent of the pivotal role of persistent pulmonary vascular pathology in COVID-19, the secondary lobular microischemia is indeed responsible for the substantial alveolar dead space of patients following COVID19, as shown by Harbut and

colleagues (1) and for the prolonged excessive angiogenesis and fibrotic remodeling of interlobular septae (2). While there is evidence for an increase of collateral ventilation in severe airway obstruction by pores of Kohn (9), the disproportion between the degree of lung consolidation and the severity of hypoxaemia may be predominantly related to redistribution of blood flow towards the bronchial circulation and intrapulmonary shunting (4,8). In addition, the rapid adaptive expansion of vascularity in the interlobular septae by intussusceptive angiogenesis may contribute to overcome and compensate the persistent hypoxaemia to a certain degree. It is notable that subsequent fibrotic extracellular remodeling is observed exactly in those interlobular septae characterized by an aberrant angiogenesis (Figure f,g) in patients recovered from acute COVID19 pneumonitis (2). In a previous study (10) on pulmonary microvascular alterations in human interstitial lung disease injury patterns, we could demonstrate the spatial coincidence of interlobular thickening and the occurrence of intussusceptive angiogenesis contributing to the initial fibrotic remodeling. Regardless of the specific mechanism of fibrotic remodeling, it is worth mentioning that the walls of secondary pulmonary lobules may be clearly identified by conventional CT scans in patients with interstitial lung diseases.

To summarize, we hypothesize that the persistence of high elevated alveolar dead space in COVID-19 convalescent patients reported by Harbut et al (1) might be linked to the indispensable adaptive response of bronchial circulation, intrapulmonary bronchopulmonary anastomosis (4,5) and blood vessel neof ormation by intussusceptive angiogenesis (2,6). These proposed mechanisms can explain the observed COVID-19 related silent hypoxaemia by defining the secondary lobule as the basic morphological unit of COVID-19 induced lung damage (2). Further investigations should be conducted to elucidate the involvement of the secondary pulmonary lobules in concert with alterations of ventilation-perfusion mismatch and increased alveolar ventilation/perfusion ratio ($V'A/Q'$) heterogeneities in alveolar dead space not only of COVID-19 patients, but in other respiratory diseases such as interstitial lung diseases (ILDs).

word count: 616 words

Figure

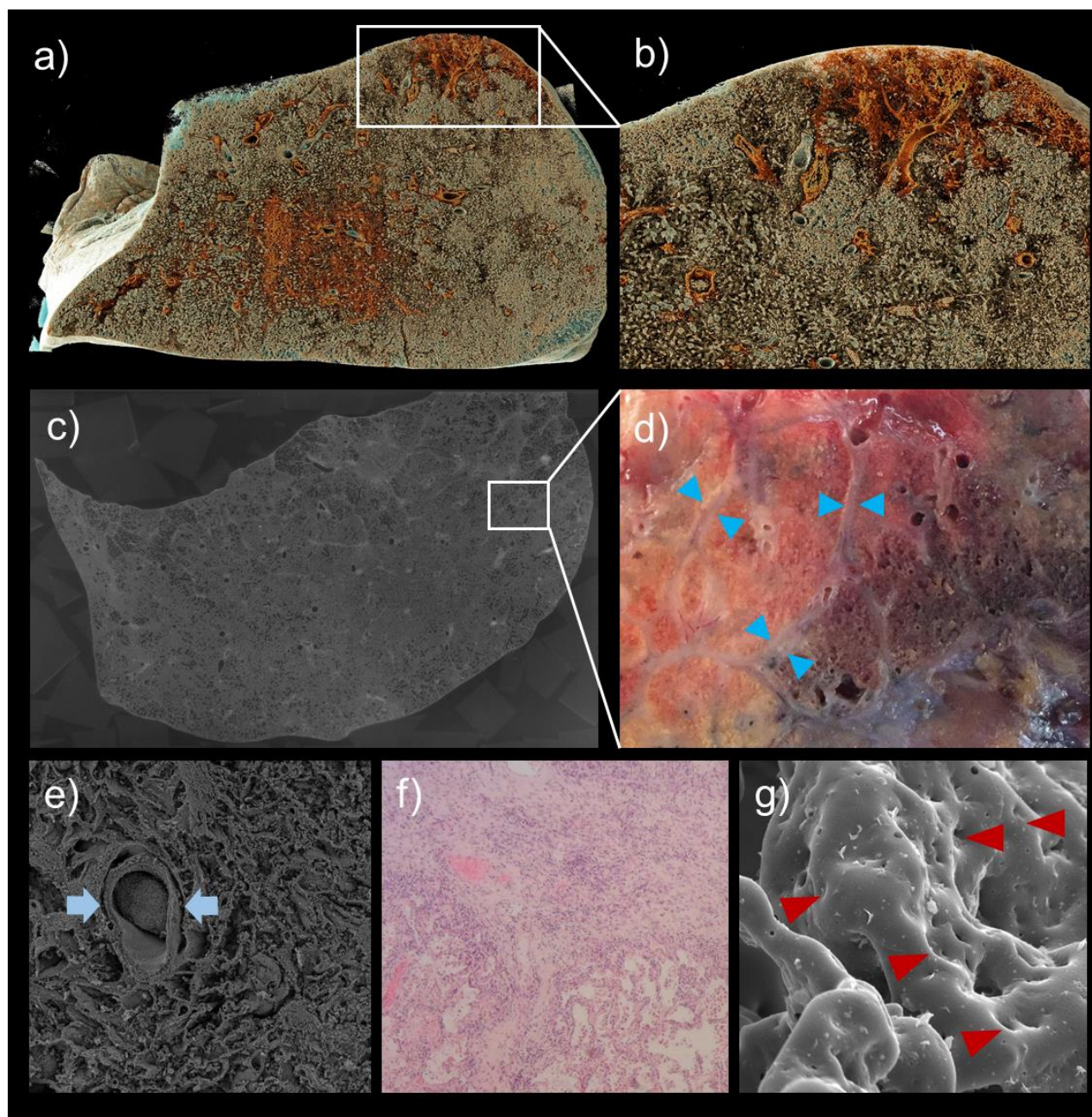


Figure Legend

(a) Cinematic Rendering of a Hierarchical Phase-Contrast Tomography (HiP-CT) study from a 78 year-old male patient who succumbed to COVID-19 highlights the spatial heterogeneity of the affected lung parenchyma. (b) Close-up of patchy subpleural consolidations reveals the heterogeneous distributions of functional alveolar dead space in COVID-19 patients. (c) Hierarchical Phase-Contrast Tomography (HiP-CT) of a COVID-19 lung imaged at 25 $\mu\text{m}/\text{voxel}$ depicts the mosaic distribution of secondary pulmonary lobules with pulmonary micro-vascular involvement and occlusions. (d) Gross appearance of an upper lobectomy of a 62yr old patient with post COVID conditions (6 months after acute COVID-19 pneumonitis) demonstrating the spatial heterogeneity of consolidated secondary pulmonary lobules. Interlobular septa with a thickness of approximately 0.1 mm (blue arrowheads). (e) Scanning electron micrograph revealed the complete occlusion of a centrilobular artery (blue arrows) and (f) a thickening of interlobular septae (HE-stained section). (g) Secondary lobular microischemia in

Long-COVID results in an even prolonged blood vessel neo-formation by intussusceptive angiogenesis (red arrowheads).

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