COVID-19 pneumonia and the pulmonary vasculature: a marriage made in hell

Peter M. George[1,2] and Sujal R. Desai[2,3]

[1]The Interstitial Lung Disease Unit, Royal Brompton and Harefield Hospitals, London, UK. [2]National Heart and Lung Institute, Imperial College London, London, UK. [3]Dept of Radiology, Royal Brompton and Harefield Hospitals, London, UK.

Corresponding author: Peter M. George (p.george@rbht.nhs.uk)

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Quantitative CT of the pulmonary vasculature is potentially important in COVID-19 associated pneumonia https://bit.ly/3vUTTRM

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Automated analysis of medical images is not new [1–3]. Researchers in the respiratory sciences and, particularly, the field of interstitial lung diseases, have long enthused about the potential for computers to analyse medical images thereby revealing "signals" hitherto invisible to the human eye: an enthusiasm only enhanced by recent developments in machine learning and artificial intelligence [4–6]. By leveraging the central importance of computed tomography (CT) scanning for diagnosis, treatment decisions and prognostication, a key aim is to identify imaging biomarkers to more accurately phenotype disease and, in so doing, move a step closer to truly patient-centric medicine. Another goal is to apply novel imaging analyses to pathogenesis, disease "behaviour" and prognostication in the hope that this might unlock new therapeutic approaches. Given the digital nature of the data and the potentially myriad imaging patterns, frequently compounded by patient, therapeutic and disease-based factors, lung imaging is ideally suited to more sophisticated analytic approaches.

In this edition of the *European Respiratory Journal*, Morris *et al.* [7] retrospectively explore the utility of automated analyses, and specifically the quantification of small blood vessels in thoracic CT scans from hospitalised patients with coronavirus disease 2019 (COVID-19) and a control cohort of COVID-19-negative patients. This approach has previously been used to study changes in the pulmonary vasculature in COPD [8] and sickle cell disease [9], to name but two clinical settings. That said, it is logical to study the small vessels in COVID-19 in view of the mounting evidence of the vasculocentric nature of this disease [10, 11]. In the reported study, the authors adopt a two-pronged approach comprising semi-quantitative visual scoring of disease extent and quantitative CT to score the proportion of blood volume in vessels of three different calibre clusters: 1.25–5 mm^2 (BV5%), 5–10 mm^2 (BV5–10%) and >10 mm^2 (BV10%). Based on previous work from the group showing that patients with COVID-19 have a decrease in the smallest blood vessels, the BV5% [12], the authors hypothesise that a BV5% reduction may be prognostic.

In line with their hypothesis, the authors report that in over 300 patients with COVID-19 from across multiple institutions in the USA, the vast majority of whom had CT appearances consistent with pneumonia, a low BV5% was associated with increased risk of mechanical ventilation or death. The authors found that a BV5% threshold of 25% conferred an odds ratio of 5.58 for mortality and 2.54 for the composite of intubation or death. The BV5% threshold of 25% remained prognostic when the visual severity score was added to the multivariate regression analysis but, interestingly, the severity score when added to age had an area under the curve of 0.87, slightly outperforming BV5% and age at 0.85 for the same composite end-point. In the control cohort of COVID-19-negative patients, the commonest imaging abnormalities were atypical/COVID-19 pneumonia (32%), non-COVID pneumonia (14%), pleural effusion (7%) and pulmonary embolism (6%). 25% of the CT scans in this group were reported as normal. BV5% was significantly lower in patients who were COVID-19-positive than the heterogenous group of

COVID-19-negative patients. The authors conclude that BV5% is a novel CT biomarker which has prognostic value, provides mechanistic insights and might stratify patients in whom anticoagulation might be beneficial.

The authors are to be congratulated for their quantitative approach which provides further support for the importance of pulmonary vascular dysfunction in severe COVID-19; an area, surely, where more knowledge is urgently required. The strengths of the study include the multicentre nature, which testifies to the generalisability of the automated analysis software across different CT scanning machines and protocols, and the large, well-phenotyped cohort of patients. As is to be expected, the study raises further questions which, at this time, remain unanswered but will hopefully provide the impetus for future work. The visually assessed severity score correlated with BV5% not only in patients with COVID-19 pneumonia, but also in the 27 patients in the control cohort with non-COVID-19-related pneumonia, and there was no significant difference in BV5% in patients with pneumonia irrespective of COVID-19 status. Furthermore, in COVID-19-negative patients with pneumonia, BV5% as a continuous variable was significantly associated with the composite of intubation or death. The implication being, therefore, that BV5% is a surrogate of disease extent and that the small blood vessels are attenuated in patients with pneumonia of *any* aetiology. Perhaps this might not be a COVID-19-specific finding but simply a reflection of vascular shunting away from regionally diseased, consolidated lung. Another potentially intriguing issue is whether the reduction in BV5% drives more severe disease or is simply a consequence of it. Finally, the finding that the visually assigned severity score is at least as effective at predicting outcomes as BV5% may prompt the cynic to ask why a quantitative approach is required at all. The authors infer that patients with limited disease on CT but a low BV5% may benefit from anticoagulation and that a low BV5% may be a prognostic marker in this setting. Clearly, the suggestion that anticoagulation may be of benefit in this group needs formal study in a controlled setting and cannot be recommended at this stage. An additional tantalising theory is that a low BV5% in early COVID-19 may predict those who will progress to develop severe and more extensive disease: if this is proven, such patients might be stratified for interventions and monitored for complications more closely. Possible associations with circulating markers of inflammation or thrombosis (such as D-dimer) are not explored by the authors and this might be an interesting follow-on study.

The above questions notwithstanding, Morris *et al.* [7] provide further evidence for the concept that the pulmonary vasculature not only bears much of the brunt of COVID-19 but also closely interacts with surrounding structures of the lung, potentially exerting pathogenic influences [13]. They also demonstrate that, despite the undeniable complexity, quantitative lung imaging is feasible, generalisable and of potential prognostic value. There are potential parallels here with the “progressive fibrotic phenotype” [14] in which predictive imaging biomarkers may be able to identify those at risk of progression; a priority research area [15]. Time will tell whether quantitative CT analyses (including artificial intelligence and machine learning), can or indeed should be integrated into routine respiratory practice. The present study represents definite progress, building on a steadily growing body of work suggesting that that this time may be approaching.

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