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Early View

Research letter

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In vivo demonstration of pulmonary microvascular involvement in COVID-19 using Dual-Energy Computed Tomography

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To the Editor,

Vascular involvement in coronavirus disease 2019 (Covid-19) has been suggested by several observations such as the high rate of pulmonary embolism [1], the prothrombotic state and the proinflammatory biological profile [2, 3] as well as the pathological findings of severe endothelial injury and diffuse thrombosis [4]. Dual-energy computed tomography (DECT) allows specific imaging of the iodinated contrast agent distribution within the lung, which has been demonstrated as a surrogate marker of lung perfusion [5, 6]. Therefore, our goal was to assess *in vivo* pulmonary microvascular involvement in patients with Covid-19 pneumonia by using DECT and to determine whether vascular changes vary during the course of the disease.

This monocentric study was approved by our institutional ethics committee. We performed a retrospective analysis of patients hospitalized for Covid-19 pneumonia (confirmed by RT-PCR for SARS-COV-2) who underwent enhanced DECT for clinical worsening of symptoms and/or hypoxemia in search of pulmonary embolism.

Lung CT angiography data were acquired on a dual-layer dual energy CT system (iQon®; Philips Healthcare) using a bolus-tracking technique with a threshold of 110 HU in the main pulmonary artery enabling iodine images reconstruction, and reviewed by a senior radiologist and a senior pulmonologist. Predominant lung lesions such as ground glass opacities (GGO) and alveolar consolidation as well as their volumetric extension per lobe (0: none, 1: 0-25%, 2: 26-50%, 3: 51-75%, 4: 76-100%) were rated. Presence and aspect of perfusion abnormalities were evaluated per lobe as an increase or decrease of perfusion blood volume (PBV) compared to the remote parenchyma. Lobar PBV was indexed to iodine concentration in the pulmonary trunk, by calculating the ratio of mean iodine concentration in a lobe to that in the pulmonary trunk. As lung perfusion may depend of the injection time, iodine concentrations ratios in the main pulmonary artery over the left atrium were recorded and expressed as median (IQ1-IQ3).

PBV distribution was tested for normality using d'Agostino-Pearson test. Student unpaired t-test was used for PBV comparisons between lobes with predominant GGO and consolidation. A multiple linear regression was used to compare the lobar PBV between parenchymal type lesions as a function of the extension. Statistical significance was set at $p < 0.05$.

Five patients were included between March 15 and April 30, 2020. All of them were men and median age was 70 years (range: 45-88). No patient had a history of chronic respiratory disease. Three patients (60%) were admitted to the intensive care unit and 1 patient (20%) died of acute respiratory failure. At the time of DECT imaging, 4 patients (80%) had oxygen supplementation therapy (oxygen saturation < 90% on room air), 2 patients (40%) had prophylactic anticoagulation therapy, while the remaining 3 (60%) had long-term therapeutic anticoagulant doses. No patient had evidence of bacterial infection.

Concurrently, D-Dimers levels were 3107 ± 3053 µg/L, fibrinogen levels were 6.5 ± 1.6 g/L, C-reactive protein levels were 93 ± 45 mg/L and platelet count was 390 000 ± 234 000/mm^3.

DECT was performed during the first week from the onset of symptoms in 2 patients (Day 7 and 8) and after 2 weeks in 3 patients (Day 17 and 18). No patient had pulmonary embolism. Patients in the early clinical phase had predominant GGO lesions (**figure 1a**) while patients in the late clinical phase had predominant consolidation (**figure 1b**). Median ratio of iodine concentration between main pulmonary artery and left atrium were calculated at 1.4 (1.3-3.1). Perfusion abnormalities were found in all lobes matching with corresponding parenchymal lesions. Mean ± SD PBV was 0.48 ± 0.09 in lobes with predominant GGO and 0.22 ± 0.08 in lobes with predominant consolidation (p<0.0001). No perfusion abnormalities were found in the areas surrounding the lesions nor in the normal parenchymal areas. Multiple linear regression analysis demonstrated a significant correlation between PBV and parenchymal lesions (R = 0.84, p<0.0001), with a positive coefficient between PBV and GGO (Pearson's r: 0.83) and a negative coefficient between PBV and consolidation (Pearson's r: -0.51) (**figure 1c**).

This pilot study has demonstrated that DECT may be used to assess pulmonary vascular involvement *in vivo* in patients with Covid-19 pneumonia. Two different patterns of lung perfusion were observed.

In the early clinical phase occurring in the first week since the onset of symptoms, the predominant parenchymal lesions were diffuse bilateral GGO and were associated with increased lung perfusion in the corresponding lobes. This observation suggests that hypoxemia in these patients may be due to a ventilation/perfusion mismatch causing pulmonary shunting. We speculate that low ventilation/perfusion ratio may be related to decreased ventilation secondary to viral pneumonia, along with normal or increased perfusion which might be due to the loss of the physiological hypoxic vasoconstriction provoked by inflammatory cytokines. These vascular changes may correspond to the histopathological findings of intussusceptive angiogenesis found in a recent autopsy study [4].

During the later phase of the disease, occurring after two weeks, the predominant parenchymal lesions were bilateral alveolar consolidation and were associated with decreased lung perfusion in the affected lobes. The presence of lung hypoperfusion in the absence of detectable pulmonary embolism is a distinctive hallmark of Covid-19 and could be due to the endothelial dysfunction and the release of prothrombotic cytokines, often referred to as « the cytokine storm » and potentially leading to acute respiratory distress syndrome. These vascular changes are corroborated by pathological findings of endothelial dysfunction, diffuse coagulopathy affecting small vessels and the formation of microthrombi [4]. All patients had increased inflammatory and prothrombotic biomarkers. It is also noteworthy that hypoperfusion lesions occurred despite anticoagulant therapy. Of note, description of pulmonary vascular manifestations of Covid-19 pneumonia using DECT has

been previously reported [7, 8]. Radiological findings were mosaic perfusion patterns, vessel enlargement within and outside of lung opacities as well as peripheral perfusion defects with surrounding halos of increased perfusion [7, 8]. These results are to a certain extent consistent with our findings. However, our study provides new insights on chronological changes in the pulmonary perfusion along the course of the disease and in relation with parenchymal CT features [9, 10].

There are limitations to our study including the small number of patients and the retrospective design. Despite the predominant opacification of the pulmonary arteries of the DECT scans, the potential participation of a systemic arterial supply within areas of pneumonia cannot be ruled out. There were no sequential DECT done in the same patient. However, CT scans were conducted for « real life » clinical purposes, taking into consideration renal and radiation risks.

Conclusion

DECT imaging demonstrated pulmonary microvascular involvement in Covid-19 pneumonia with two distinctive patterns. It may be used to better understand Covid-19 pathophysiology and herald new targets for therapeutic trials.

Aknowledgements

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Figure Legend

Key imaging features of microvascular involvement in COVID-19 using lung angiography dual-energy CT scans.

Perfusion blood volume (PBV) is defined as the ratio between iodine concentration in a pulmonary lobe over iodine concentration in the main pulmonary artery.

1a. Representative imaging features of the early clinical phase: increased perfusion blood volume (PBV) is seen (black arrows, right panel), matching with ground glass opacities (GGO)(black arrows, left panel), relatively to the areas without GGO.

1b. Representative imaging features of the late clinical phase: decreased PBV is seen (white arrows, right panel), matching with alveolar consolidation (black arrows, left panel), relatively to the areas without condensation.

1c. 3D graph of lobar PBV as a function of the presence and extension of GGO and alveolar consolidation. Each dot corresponds to a lobe, the coordinates of which are represented by PBV in the z axis, GGO extension in x axis and consolidation extension in y axis (volumetric extension score, 0: none, 1: 0-25%, 2: 26-50%, 3: 51-75%, 4: 76-100%). Color grid represents the multiple linear regression plane.

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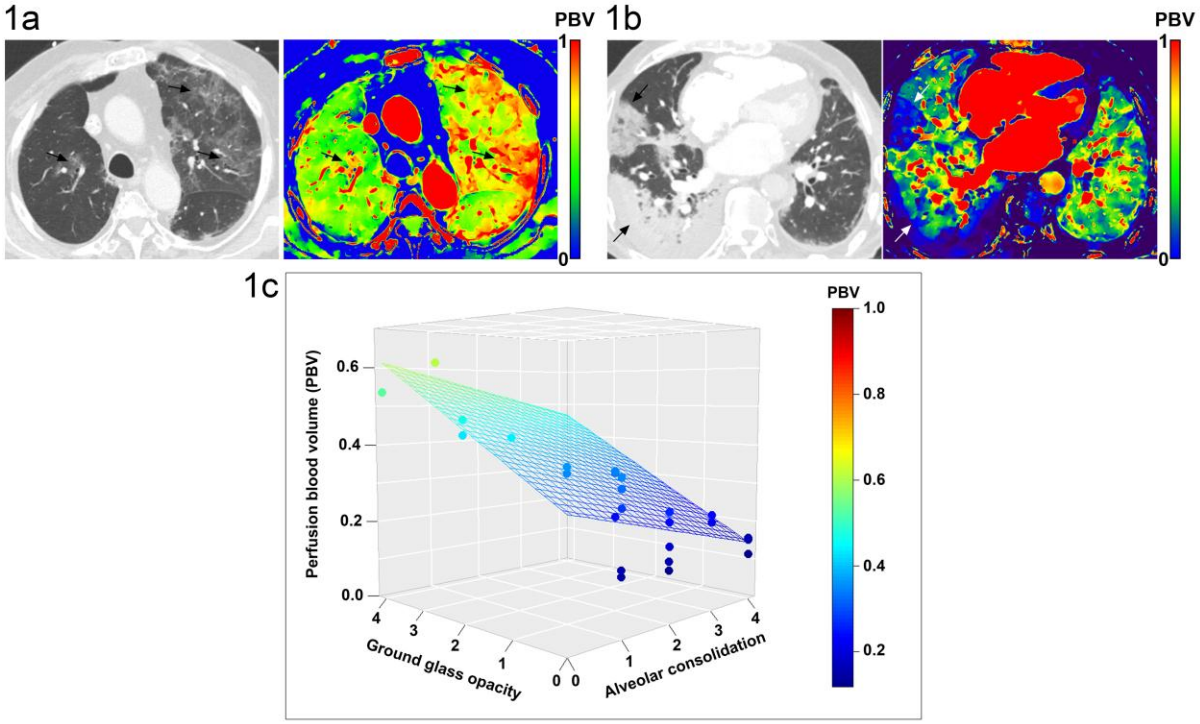
1a
PBV
1
0
1b
PBV
1
0
1c
PBV
1.0
0.8
0.6
0.4
0.2
Perfusion blood volume (PBV)
0.6
0.4
0.2
0.0
4
3
2
1
0
Ground glass opacity
0
1
2
3
4
Alveolar consolidation