Spectrum of Vascular Involvement in Coronavirus Disease 2019 Pneumonia—Findings on CT Perfusion

Jan H. von der Thüsen, MD, PhD; Elyas Ghariq, MD; Maria J. Overbeek, MD, PhD; Eliane Leyten, MD, PhD; Tessa Drijkoningen, MD, PhD; Hester A. Gietema, MD, PhD; Mathias Prokop, MD, PhD; Henriette M. E. Quarles van Ufford, MD, PhD

Objectives: There is accumulating evidence of a distinct coagulopathy in severe acute respiratory syndrome coronavirus 2 infection which is associated with poor prognosis in coronavirus disease 2019. Coagulation abnormalities in blood samples resemble systemic coagulopathies in other severe infections but demonstrate specific features such as a very high D-dimer. These clinical observations are consistent with histopathologic findings of locally disturbed pulmonary microvascular thrombosis and angiopathy in end-stage coronavirus disease 2019. However, exact underlying processes and the sequence of events are not fully understood.

Data Sources: CT perfusion may provide insight in the dynamic aspect of the vascularity in pulmonary lesions in coronavirus disease 2019 infection as, in contrast to dual energy CT, a multiphase perfusion pattern is displayed.

Study Selection: In six patients with coronavirus disease 2019 pneumonia, findings on additional CT perfusion series were correlated with known histopathologic vascular patterns upon pulmonary autopsy of patients who had died of coronavirus disease 2019.

Data Extraction: In this case series, we were able to show perfusion changes on CT scans in typical pulmonary lesions illustrating diverse patterns.

Data Synthesis: We demonstrated hyperperfusion in areas with ground glass and a severely decreased perfusion pattern in more consolidated areas often seen later in the course of disease. A combination was also observed, illustrating temporal heterogeneity.

Conclusions: These findings provide new insights into the pathophysiology of coronavirus disease 2019 pneumonia and further understanding of the mechanisms that lead to respiratory failure in these patients.

Key Words: coronavirus disease 2019; CT perfusion; hyperperfusion; pneumonia; thrombosis

Evidence of a distinct coagulopathy in severe acute respiratory syndrome coronavirus 2 infection is accumulating, setting it apart from other viral respiratory tract infections. Reports of severe coronavirus disease 2019 (COVID-19) demonstrate cumulative occurrence rate of pulmonary thromboembolic complications and their causative role in clinical deterioration (1–4). These clinical observations are consistent with histopathologic findings of microvascular thrombosis and angiopathy in end-stage COVID-19 lung (5). However, the precise pathophysiology and pathobiology is not fully understood.

Typical findings on chest CT in COVID-19 pneumonia include ground glass opacities with multifocal bilateral distribution in regions close to visceral pleural surfaces (6, 7). Dilated vessels (> 3 mm diameter) entering ground glass opacities is another characteristic finding, interpreted as a thromboinflammatory process (2, 6). CT perfusion (CTP) may provide insight in the dynamic aspect of the vascularity in pulmonary lesions in COVID-19 infection as, in contrast to dual energy CT, a multiphase perfusion pattern is displayed (8). Therefore, CTP series may improve understanding of pathophysiologic mechanisms in developing thromboembolic and microvascular thrombotic complications.

In this article, we observe and interpret CTP patterns of COVID-19 pulmonary features. To improve understanding of CTP patterns and underlying pathophysiology, results are correlated with known histopathologic vascular patterns in autopsy cases with COVID-19 pneumonia (9).
MATERIALS AND METHODS

Six patients with COVID-19 pneumonia in different disease stages were retrospectively studied. Because of suspected pulmonary thromboembolic complications, CT angiography (CTA) was performed with additional CTP series. All patients signed consent for the use of their data for this study, and all data were acquired in the context of routine patient care. A formal study protocol was not required, following waiver by the institutional review board (reg. no G20.080). CTP was performed in an 8.5 cm thick slab placed at most prominent pathologic areas accessible for evaluation, including the aorta, pulmonary artery, left ventricle, and normal lung parenchyma for postprocessing. The sequential low-dose acquisition of this slab was performed after injection of 40 mL iodinated contrast at 5 mL/s. Postprocessing was done using dual-input 4D lung perfusion on a Vitrea dedicated workstation (Vitrea; Canon Medical Systems, Otawara, Japan). Perfusion maps were reconstructed using systemic arterial flow (AF) via the bronchial arteries and pulmonary artery flow (PF) (in mL/min/100 mL). Hypo- and hyperperfusion were defined relative to morphologically normal lung parenchyma. Perfusion patterns were described as PF/AF pairs: double hyperperfusion if for both PF and AF; hyperperfusion was present in the affected area, mixed perfusion if PF was reduced but AF was increased, and double hypoperfusion if both PF and AF were reduced. The observations on CTP were put in relation to CTA findings and previous scans, if available.

CT findings in lung parenchyma were classified as low-density ground glass opacity in opacities with an attenuation less than –600 Hounsfield Units (HU), and high-density ground glass opacity with an attenuation of at least –250 HU. We also analyzed crazy paving (ground glass opacities with reticulation) and consolidations.

Direct correlation of CT patterns and histopathologic findings in COVID-19 is difficult. We used the combination of morphologic CT and CTP findings to find corresponding histopathologic patterns in lung tissue from four patients who had died of COVID-19 pneumonia that could explain the CT phenotypes.

RESULTS

We included six patients with reverse transcription polymerase chain reaction-proven COVID-19 infection; median age 62.6 years (range 43–73 yr) and median duration of symptoms at time of CTP 16.2 days (range 4–29 d).

On CTP, we found three distinct perfusion patterns in COVID-19 lesions. A double hyperperfusion pattern, via the bronchial arteries, was seen in areas of low-density ground glass opacities (Fig. 1, first column) and present in all six patients. The affected regions showed dilated vessels entering the ground glass opacities. These vessels were patent and well-opacified on CTA (Fig. 2). Histopathologic findings corresponding to this pattern may be dilated pulmonary arteries in regions with microvascular dilation in the context of acute interstitial pneumonia (Fig. 1, first column).

A double hypoperfusion pattern was seen in five patients (Fig. 1, second and third columns). This pattern was present in this series past day 10. It occurred in dense ground glass opacities and consolidations, with or without features of organizing pneumonia and without obvious dilatation of entering vessels. All dense ground glass opacities and consolidations showed abnormal perfusion with heterogeneous aspects. Pathologic findings that correspond with this CT pattern may be microvascular damage and thrombosis with ensuing infarction, intra-alveolar fibrin exudates, and hemorrhage (Fig. 1, second and third columns).

In four of six patients, a combination of CT patterns was present (Fig. 1, second and fourth columns), corresponding with pathologic findings showing coexistence of patterns associated with earlier and later disease stages in the same patient.

A mixed perfusion pattern was seen in dense ground glass opacities in one patient (Fig. 1, fourth column), without dilatation of the vessel entering the ground glass opacities. Corresponding histopathologic findings are likely related to occlusion of larger arterial structures due to in situ thrombus formation related to (possibly virus-induced) vascular damage with endotheliitis or thromboembolic occlusion (Fig. 1, fourth column).

A combination of ground glass opacities with increased perfusion and consolidations with decreased perfusion was displayed in the same patient (data not shown), a finding also observed in histopathology and illustrating temporal heterogeneity.

Pulmonary CTA displayed (sub)segmental pulmonary embolisms, with thromboembolic aspect in two patients, with a prolonged disease course (25 and 28 d, respectively) and elevated D-dimer (7.17 and 20.54 mg/L). In CTP, no pulmonary lesion was located in the region distal to the emboli.

DISCUSSION

In this case series, we demonstrated a diverse pattern of perfusion changes in typical pulmonary lesions on CTP of patients with COVID-19 pneumonia. First, hyperperfusion through a dilated capillary system in ground glass opacities of low-to-moderate density was displayed. This is commonly observed in early inflammatory response in viral infections and also described in COVID-19 histopathology. Enlarged vessels entering ground glass opacities early in the disease course is a common finding in COVID-19 (5–7), suggested to occur due to hyperemia instead of pulmonary thrombosis, as no filling defects on corresponding CTA were observed. This double hyperperfusion pattern might explain some of the hypoxia encountered by COVID-19 patients: instead of preventing perfusion of the lung in poorly ventilated areas, we see increased flow, resulting in shunting of poorly oxygenated blood. Interestingly, the reported hyperperfusion in ground glass opacities supports the hypothesized role of the angiotensin-converting enzyme-2-regulated kallikrein-bradykinin system in COVID-19 pneumonia pathophysiology (10). Increased activation of bradykinin receptors induces a.o. vasodilation, which is precisely our observation in CTP: a double hyperperfusion pattern in ground glass opacities.

Second, in a prolonged disease course, ground glass opacities become denser with hypoperfusion on corresponding CTP, suggesting obstruction or occlusion of small arteries. This may correspond to microvascular thrombus formation and intra-alveolar extravasation, as seen in areas with fibrinous exudates and acute fibrinous organizing pneumonia and described in COVID-19 pneumonia (9). A combination of ground glass opacities with increased perfusion and consolidations with decreased perfusion was also displayed in the same patient, which illustrates the heterogeneity of the disease, with varying involvement of pulmonary and bronchial arterial systems.

This study also supports the notion of a diseased pulmonary microvasculature later in the disease course, as on CT, areas with more...
Figure 1. Spectrum of pulmonary lesions on CT, CT perfusion (CTP), and histopathologic findings related to time after onset of symptoms. The top section provides a summary of findings. The first imaging row (CT) shows areas with ground glass opacities. In the second and third rows, the corresponding pulmonary and systemic perfusion in these areas is demonstrated. Areas of hyperperfusion on CTP are annotated by red ellipses, areas of hypoperfusion are denoted by blue ellipses. Bottom section: Corresponding vascular patterns frequently seen in the histopathologic spectrum of coronavirus disease 2019 pneumonia. First column, patient A (day 4): double hyperperfusion pattern in a ground glass opacity in the left upper lobe. This is likely to correspond with an acute interstitial pneumonia (AIP) with vascular dilatation and edema (*) (and in this case also influx of intravascular megakaryocytes (arrow)). Second column, patient B (day 10): double hyperperfusion pattern in a ground glass opacity in the right upper lobe. By contrast, a double hypoperfusion pattern in the dense ground glass opacity in the left upper lobe. A similar pattern is seen in the apex of the right lower lobe (not highlighted). These findings may correspond respectively with AIP as above and microvascular thrombotic occlusion (MVT) in alveolar capillaries (arrows) with fibrinous exudates with acute fibrinous and organizing pneumonia (AFOP) pattern in surrounding alveoli (**). Third column, patient C (day 28): double hyperperfusion pattern in a subpleural ground glass opacity in the right upper lobe and double hypoperfusion pattern in a consolidation in the left upper lobe. Histologic patterns are likely to include AIP and MVT. Fourth column, patient C (day 28): mixed perfusion pattern in a subpleural consolidation in the right upper lobe with double hypoperfusion pattern in left upper lobe. In addition to AIP and MVT, histology may show in situ thrombosis as displayed in third column: eccentrically located thrombus (arrows) adjacent to an area of vascular damage and cellular proliferation in a pulmonary artery, with residual patent lumen (*). Alternatively, there may be an occluding thromboembolism in a (sub)lobar pulmonary artery. BiPAP = biphasic positive airway pressure.
consolidations and reduced perfusion are then seen, and in histopathology, microthrombi are observed (4). The temporal heterogeneity in the (density- and) perfusion patterns in this phase may reflect the complex nature of COVID-19–related coagulopathy, not previously seen in viral pneumonias (2). However, despite intensive (mono)anticoagulation therapy, incidence of pulmonary vascular complications in COVID-19 is high. Therefore, the development of therapeutic strategies interfering early in the inflammatory phase of the disease, as to possibly prevent a disturbed interplay between the inflammatory and hemostatic environment, may constitute an attractive potential avenue of treatment. In turn, the vascular dilation and subsequent leakage induced by activation of bradykinin receptors and local inflammation may also activate the intrinsic coagulation cascade and local fibrin production, causing microvascular obstruction. Therefore, the bradykinin receptor might be an interesting target to be explored. More study of the underlying mechanisms of formation and composition of microvascular obstructive components in this distinct COVID-19 patient group is required.

This study has several limitations. First, CTP is not a validated technique for assessment of perfusion in pneumonia, although CTP is described in pulmonary nodules and malignancies and is commonly used in brain imaging (8). Second, pulmonary emboli may hinder interpretation of lung perfusion of specific lesions in this case series; however, in four patients, no pulmonary emboli were detected. In two patients, pulmonary emboli were detected outside the perfusion slab. As a third limitation, this pilot included only six patients. However, we were able to suggest perfusion patterns of the typical pulmonary COVID-19 CT features. Fourth, histology was obtained from a separate cohort. Nevertheless, we did find vascular patterns in CTP that could be matched to known pathologic findings in COVID-19. Finally, as the perfusion series is performed at one moment in time, true temporal development of changes in perfusion of the pulmonary lesions is not displayed.

CONCLUSIONS
The presented findings in CTP indicate biphasic pulmonary vascular dilation and obstruction and a broad spectrum of involvement at the microvascular level, corresponding with known histopathologic findings in COVID-19 pneumonia. More detailed assessment of vascular and perfusion changes is needed to increase understanding of the vascular involvement in COVID-19 disease and to develop tailored therapeutic strategies for different disease phases.

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For information regarding this article, E-mail: j.vonderth usen@erasusmc.nl

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