Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Extensive pulmonary perfusion defects compatible with microthrombosis and thromboembolic disease in severe Covid-19 pneumonia

Dear Editors,

It is unclear why some patients with progression to severe COVID-19 pneumonia require admission to an intensive care unit (ICU) for invasive mechanical ventilation while others can be managed with supplementary oxygen on the ward [1]. Several hypotheses have been proposed to explain the differences in clinical course between patients. One hypothesis is that pulmonary embolism results in severe hypoxemia. Observational studies suggest a high incidence of deep vein thrombosis in COVID-19, up to 25% in ICU patients compared to 6.5% in ward patients [2], which may progress to pulmonary embolism. Pulmonary edema as a result of dysbalance of the bradykinin-kallikrein system is also suggested to contribute [3]. Another hypothesis is the onset of local thrombosis in the pulmonary microvasculature due to an inflammatory thrombotic microangiopathy [4].

We hypothesized that patients requiring invasive mechanical ventilation for COVID-19 related acute respiratory failure have more extensive perfusion defects compared to patients not requiring invasive ventilation.

We performed an observational study in 20 consecutive patients who were admitted after March 15th 2020 to a university hospital in the Netherlands with RT-PCR confirmed COVID-19, and who in the course of the disease had a clinical suspicion of pulmonary embolism for which they underwent CT pulmonary angiography (CTPA). This suspicion could be either at the emergency department or later during admission. All patients underwent a dual energy CTPA, for the ICU patients primarily on clinical grounds (Gestalt), for the ward patients according to the YEARS-criteria [5]. Baseline non-enhanced chest CT performed on presentation at the emergency department were regarded non-suitable for PE-evaluation. We compared 10 consecutive patients with severe COVID-19 pneumonia who were admitted to the ICU requiring mechanical ventilation because of type I respiratory failure to 10 consecutive patients who were managed on the ward with supplemental oxygen with a maximum of 15 L/min via non-rebreathing mask but without need for positive pressure ventilation. All patients had radiological characteristics of COVID-19, scored as CORADS 5 according to the “COVID-19 Reporting and Data System” [6]. CO-RADS 5 implies a very high level of suspicion of pulmonary COVID-19 based on typical CT findings (multifocal bilateral ground-glass opacities with or without consolidations in lung regions close to pleural surfaces). Informed consent was waived by the institutional ethics committee.

Clinical data were obtained through review of medical records. Patient characteristics (age, sex, comorbidities), clinical follow up and RT-PCR results were extracted from electronic patient records. The data reported are those available through May 15th, 2020. Results are reported according to the STROBE guideline.

CT-images were acquired from a high-end dual source CT (CT Somatom Force, Siemens Healthineers, Forchheim, Germany) in the emergency department after injection of 50 mL contrast medium (Iomeron 300, Bracco Imaging, Germany) at 5 mL/s in the right antecubital vein, with the following scan parameters: collimation $2 * 192 * 0.6$ mm, 80/Sn150 kVp, Qref mAs 90/50, 1 and 3 mm lung and soft kernel reconstructions. Postprocessing for iodine maps was performed on a dedicated software platform (Lung Analysis, Syngo via, VB30, Siemens Healthineers, Forchheim, Germany). All images were evaluated independently by two radiologists, differences were settled in consensus. Images were primarily read in axial, coronal and sagittal orientations in PACS (Enterprise Imaging, AGFA-Gevaert, Mortsel, Belgium). Pulmonary embolism was defined as a constant intravascular filling defect on CTPA. Location of a filling defect was registered for each lobe until most distal subsegmental levels, occurrence of an isolated subsegmental defect and central emboli were also noted separately. Severity of the COVID-19 pneumonia was assessed semi-quantitatively for each lobe in steps of 25% (0: normal; 1: $< 25\%$; 2: $< 50\%$; 3: $< 75\%$ and 4 $> 75\%$ of lobe volume involved) with a maximum score of 20. Iodine maps were calculated for Pulmonary Blood Volume (PBV) using Lung analysis. Pulmonary blood volume perfusion defects were visually assessed semi-quantitatively on the orange coloured iodine distribution maps in steps of 10% for each lung. The following parameters suggestive of right ventricular dysfunction were assessed: right-to-left ventricular (RV/LV) ratio, pulmonary trunk diameter, bowing of the interventricular septum and reflux of contrast medium. All data were registered on a specially designed CRF. Data are presented as mean $\pm$ standard deviation (SD) for normally distributed variables and median $\pm$ interquartile ranges (IQR, 25th to 75th percentile) for non-normally distributed variables. All statistics were performed in SPSS version 26 (SPSS Inc., Chicago Ill).

Median duration between disease onset and CTPA were 16 (IQR 11) and 13.5 (IQR 10) days for the ICU and ward-groups, respectively. Pulmonary embolism was diagnosed in 8 ICU patients and in 2 patients managed on the ward. Central emboli were observed in 2 ICU patients and 1 ward patient (Table 1).

All ICU patients showed large areas of scattered perfusion defects throughout both lungs, not only at the subpleural regions but also in the deeper parts of the lungs remote from the pleura or fissures. The areas with perfusion defects were anatomically not completely explainable by pulmonary embolism and parenchymal involvement. Ward patients only showed small perfusion defects near the pleura or directly associated with a pulmonary embolism. (Supplement Fig. 1) Estimated mean percentage of perfusion defects was 52.5% $\pm$ 14.8 in ICU patients and 17.5% $\pm$ 7.5 in COVID-19 ward patient (Fig. 1). A lower pulmonary blood volume was seen in ICU patients (1404 mL) compared to ward patients (2039 mL) (Supplement Fig. 2). Enhancement of pulmonary trunk and aorta was not different between the 2 groups. No significant differences were present between the groups with respect to signs of right ventricular dysfunction.

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Table 1
Characteristics of ICU and ward patients with severe COVID-19 pneumonia who underwent CT pulmonary angiography.

CT attenuation	ICU		Ward	
CT Severity *points* (max20; mean, SD)	17.7	(2.0)	8.5	(3.8)
Ascending aorta *HU* (median, IQR)	261	(109)	256	(151)
Pulmonary trunk *HU* (median, IQR)	295	(156)	365	(138)
CT angiography results				
Pulmonary embolism				
Present (N; %)	8	(80)	2	(20)
Bilateral (N; %)	5	(50)	1	(10)
Most proximal clot location				
Central (N; %)	2	(20)	1	(10)
Segmental (N; %)	4	(40)	0	(0)
Subsegmental (N; %)	1	(10)	1	(10)
Isolated subsegmental (N; %)	1	(10)	0	(0)
Signs of right ventricular dysfunction				
Right/Left Ventricular ratio > 1.0 (N; %)	3	(30)	3	(30)
Pulmonary Trunk > 29 mm (N; %)	4	(40)	2	(20)
Septal flattening (N; %)	2	(20)	1	(10)
Reflux of contrast medium (N; %)	2	(20)	1	(10)
Perfusion defects Iodine map				
Right lung *% of lung* (mean, SD)	52.0	(16.2)	21.0	(5.7)
Left lung *% of lung* (mean, SD)	52.0	(16.2)	20.0	(10.5)
Total *% of both lungs* (mean, SD)	52.5	(14.8)	17.5	(7.5)
Perfusion defect > 1/3 lung volume (N; %)	10	(100)	0	(0)
Pulmonary blood volume right lung	838	(669)	1209	1527
Pulmonary blood volume left lung	536	(490)	895	(1289)
Pulmonary blood volume lungs	1404	(1423)	2039	(2934)

The high incidence of pulmonary embolism we observed is in line with the reported incidences of venous thromboembolic events in several cohorts of COVID-19 patients [2,7,8]. Despite this fact, our observation that the minority of cases had central pulmonary embolism suggest that the pulmonary emboli are not all the result of deep vein thrombosis migrating to the pulmonary vasculature. Local microthrombi might better explain our observations and might result from diffuse alveolar damage and local thrombotic microangiopathy, which is in line with a case series of post mortem COVID-19 sections of the lungs [9]. This is not unique for COVID-19 pneumonia as acute infections in general are associated with an increased risk of venous thromboembolic events. The pathophysiology of thrombotic coagulopathy is complex and multifactorial, involving an interplay between cellular and plasmatic elements of the hemostatic system and components of the innate immune response to the infecting pathogen [10]. This study emphasizes the need for a better understanding of this interplay in severe COVID-19 pneumonia. Whether a more aggressive therapeutic anticoagulation strategy at an earlier stage must be installed to prevent severe thrombotic events in – and outside the pulmonary system is unclear and should be further evaluated in randomized controlled trials.

Absent perfusion in normally aerated lung tissue is detrimental, certainly in the context of pneumonia, as it will cause additional dead space ventilation and may redirect pulmonary blood flow to poorly aerated lung tissue resulting in additional shunt and hypoxemia. The large areas of severely diminished perfusion most likely reflect diffuse pulmonary microcirculation dysfunction that is irrespective of the presence of pulmonary embolism. Our findings are consistent with a recent case report that also suggested vascular and perfusion abnormalities in severe COVID-19 pneumonia, [4] although the extent of the perfusion defects is much more evident in this present study.

The strength of our study is that all patients underwent advanced imaging using a high-end dual source CT-scanner dedicated to COVID-19 patients. This limits the chance of measuring artifacts, although even then technical challenges remain. Our study also has several limitations. First, this is a single center study using a cross sectional design which does not allow to make any causal inferences with regard to the pathophysiology or order of events. Although basis for suspicion of PE was the same, as for the ICU patients evaluation was ordered primarily on clinical grounds and mostly at a later stage, and for the ward patients according to the YEARS-criteria mostly (but not always) at presentation, we cannot exclude confounding differences between the two groups. Second, we used semi-quantitative scores for single pass CT

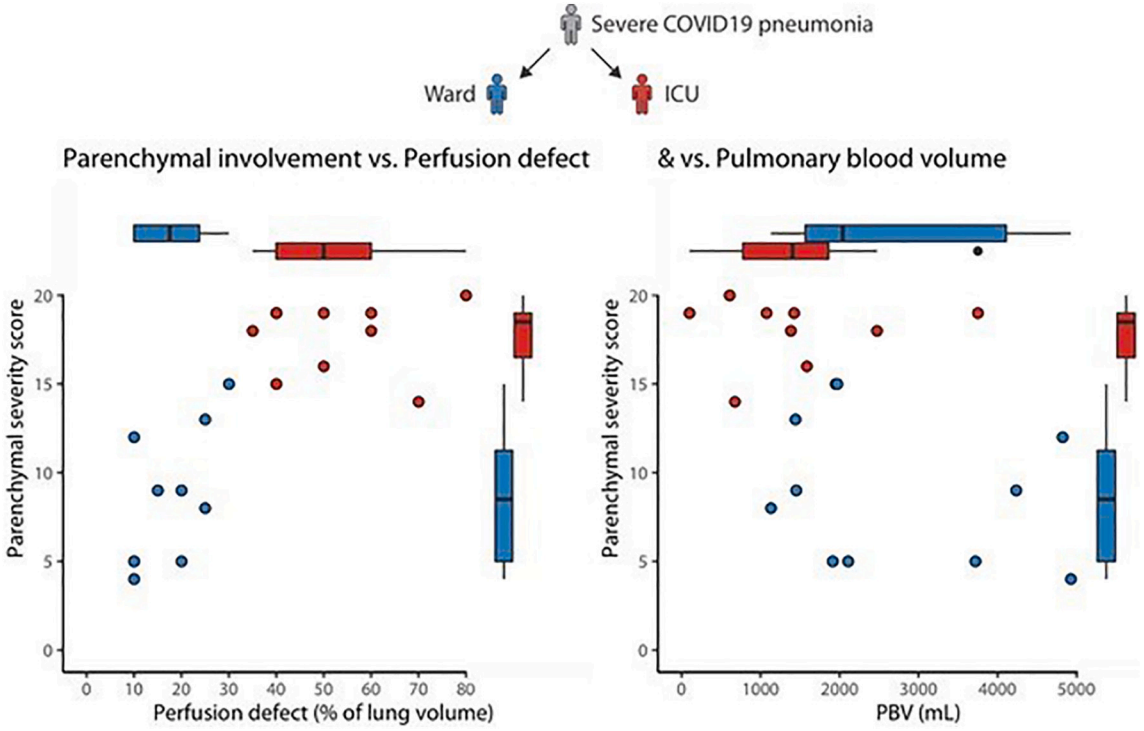

Fig. 1. Relationship between parenchymal involvement, perfusion defect, pulmonary blood volume for intubated ICU patients (red) and ward patients (blue). Y-axis: Parenchymal involvement with maximal score 20. Left panel, x-axis: perfusion defect as percentage of lung volume. Right panel, x-axis: pulmonary perfused blood volume (PBV) in mL. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

perfusion evaluation. Quantitative measurements for image analysis require a time-consuming procedure, and also are not validated for the investigated questions. Next, we did not prospectively calculate the dead-space and shunt fractions in the included patients and were unable to link the imaging results with gas-exchange. Finally, we cannot assess the impact of positive pressure ventilation on the observed perfused blood volumes and perfusion defects. Although the effect of positive pressure ventilation on lung perfusion is well known, little data is available on the changes in regional perfusion defects like we observed.

In conclusion, invasively mechanically ventilated ICU patients with severe COVID-19 not only can develop pulmonary embolism but also show large scattered areas of severely diminished perfusion consistent with diffuse pulmonary microcirculatory dysfunction. These defects seem to be independent of the presence of pulmonary embolism, possibly reflective of microthrombi in the pulmonary circulation. The combination of extensive parenchymal involvement with diffuse perfusion abnormalities may explain the occurrence of severe and persistent respiratory failure that is frequently seen in patients with severe COVID-19 pneumonia who require mechanical ventilation.

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Availability of data and material (data transparency)

Not applicable.

Declaration of competing interest

No conflicts of interest relevant to the work submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.08.026.

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