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.

Progressive respiratory failure in COVID-19: a hypothesis

The coronavirus disease 2019 (COVID-19) pandemic is a challenge for intensive care units (ICUs) worldwide because of the large numbers of patients, a scarcity of resources, the poor prognosis of patients they treat, and uncertainty regarding the disease's pathogenesis. The first case of COVID-19 in the Netherlands was confirmed on Feb 27, 2020, and the patient was put on mechanical ventilation in our ICU department at Erasmus Medical Center (Rotterdam, Netherlands). Currently, our department is the largest COVID-19 ICU in the Netherlands. We would like to share our findings regarding a possible mechanism of progressive respiratory failure.

From the date of the first confirmed case up to April 5, a total of 90 patients were admitted to our ICU, most of whom were male (n=68 [76%]), of older age (mean age 62 years [SD 14]), and obese (mean body-mass index 29 kg/m^2 [SD 5]). Treatment consisted of prone positioning, low tidal volumes, positive end-expiratory pressure (PEEP) titration according to the higher PEEP, lower fraction of inspired oxygen table,[1] and restrictive fluid management. These methods resulted in low driving pressures, no pneumothoraxes, low vasopressor doses, and weaning from mechanical ventilation approximately 2 weeks after ICU admission. However, some patients (n=17 [19%]) deteriorated within 2 weeks and no longer responded to prone positioning. All of these patients had major pulmonary embolism established by lung CT or cardiac ultrasound.

Initially, patients with COVID-19 on our ICU developed increased alveolar capillary permeability and subsequent interstitial oedema. The presence of oedema is illustrated by ground-glass opacities of the lung parenchyma on lung CT.[2] If patients require mechanical ventilation, oxygenation improves following prone positioning, higher PEEP, and restrictive fluid management. Subsequently, their condition might deteriorate suddenly, and pulmonary embolism can occur, detected by contrast-enhanced lung CT scan.[3] On our ICU, five further patients had progressive respiratory failure, in whom we did lung CT and found pulmonary embolism, either located centrally or segmentally, in all cases. In addition, we were confronted with these patients developing deep venous thrombosis, and frequent coagulation of renal replacement therapy filters. We hypothesise that the patients with COVID-19 with pulmonary embolism entered a hypercoagulable state with endothelial activation following an increase in proinflammatory cytokines.

An association between increased coagulation status and increased capillary permeability might exist. A plasma D-dimer concentration greater than 4 µg/mL, combined with increasing inflammatory markers such as interleukin-6 (IL-6), and loss of response to prone positioning might be useful parameters to identify patients at risk of pulmonary embolism. Based on our early findings in our first 90 patients with COVID-19, we now include D-dimer and IL-6 in our routine laboratory tests in patients with COVID-19, and increase the prophylactic dose of low-molecular-weight heparin (nadroparin 5700 IU subcutaneously, from once a day to twice a day).[4] In addition, we do a lung CT even at a low level of suspicion of pulmonary embolism, and we encourage others to do the same.

In summary, COVID-19 might be associated with hypercoagulability, and clinicians should consider a pulmonary embolism in cases of progressive respiratory failure.

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Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT

Studies have shown that some patients with coronavirus disease 2019 (COVID-19) and acute hypoxaemic respiratory failure have preserved lung compliance, suggesting that processes other than alveolar damage might be involved in hypoxaemia related to COVID-19 pneumonia.[1] The typical imaging features of COVID-19 pneumonia, including peripheral ground-glass opacities with or without consolidation, are also non-specific and can be seen in many other diseases.[2] There has been increasing attention on microvascular thrombi as a possible explanation for the severe hypoxaemia related to COVID-19.[3,4]

Dual-energy CT imaging can be used to characterise lung perfusion and is done as part of the standard protocol for imaging pulmonary embolism at our institution. Three patients with COVID-19, as confirmed by nasopharyngeal RT-PCR at our

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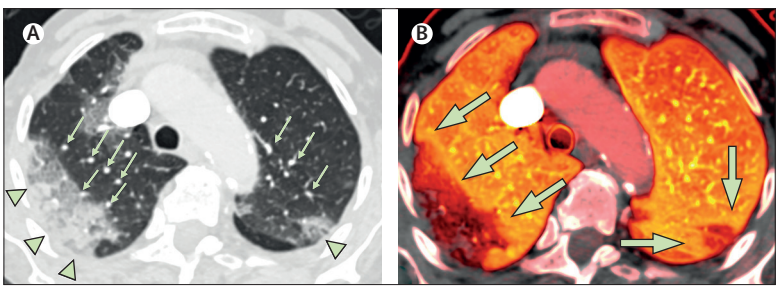

***Figure*: Dual-energy CT in a patient with COVID-19 pneumonia without evidence of pulmonary emboli**
Patient 1, an 87-year-old woman with a history of fever and cough for 5 days, was found on the floor of her nursing home. On admission to hospital, the patient required a non-rebreather mask with a flow rate of 15 L/min to maintain an oxygen saturation of 85%; intubation was not pursued as the patient's status was comfort measures only. (A) There is a large area of peripheral ground-glass opacity and consolidation within the right upper lobe and smaller ground-glass opacity in the posterior left upper lobe (green arrowheads), which are accompanied by dilated subsegmental vessels proximal to, and within, the opacities (green arrows). (B) The accompanying image of pulmonary blood volume shows corresponding wedge-shaped areas of decreased perfusion within the upper lobes, with a peripheral halo of higher perfusion (green arrows). COVID-19=coronavirus disease 2019.

hospital, who did not have a history of smoking, asthma, chronic obstructive pulmonary disease, or other pulmonary conditions, underwent dual-energy CT imaging for elevated concentrations of D-dimer (>1000 ng/mL) and clinical suspicion of pulmonary emboli. Although no pulmonary emboli were observed in these individuals, we noted striking perfusion abnormalities that have not been previously described; in retrospect, at least nine other COVID-19 cases also shared these findings. In addition to the typical CT features of COVID-19 pneumonia,[2] we observed considerable proximal and distal pulmonary vessel dilatation and tortuosity, predominately within, or surrounding, areas of lung opacities. Here, we present the first published images from dual-energy CT imaging of COVID-19 pneumonia that show profound vascular and perfusion abnormalities (figure; appendix).

See **Online** for appendix

Three major findings from dual-energy CT were observed on the images of pulmonary blood volume perfusion: preferentially increased perfusion of the lungs proximal to areas of lung opacity, decreased areas of peripheral perfusion corresponding to peripheral lung opacities, and a halo of increased perfusion surrounding peripheral areas of consolidation. The observed pulmonary vascular dilation might be due to relative failure of normal, physiological hypoxic pulmonary vasoconstriction in the setting of overactivation of a regional vasodilatation cascade as part of a dysfunctional and diffuse inflammatory process. Additionally, the mosaic perfusion pattern did not correspond to findings of bronchial wall thickening or secretions, making airway disease as the main underlying cause of hypoxaemia unlikely. Therefore, these perfusion abnormalities, combined with the pulmonary vascular dilation we observed, are suggestive of intrapulmonary shunting toward areas where gas exchange is impaired, resulting in a worsening ventilation–perfusion mismatch and clinical hypoxia. Although peripheral opacities with hypoperfusion can be seen in pulmonary infarction, no pulmonary emboli were observed in any of the studies, and segmental increased perfusion to areas of infarction would be very atypical. Furthermore, a peripheral halo of increased perfusion has not been described in pulmonary infarction, but has been described once previously in a case of bacterial pneumonia.[5] However, blood and sputum cultures were negative in the three patients with COVID-19 at our hospital and did not suggest bacterial coinfection. It might be possible that the inflammatory response to COVID-19 resembles more of a bacterial infection than a viral infection. Overall, the combination of these imaging findings is novel for COVID-19 pneumonia.

Treatment for acute respiratory failure in patients with COVID-19 is challenging in part because of little understanding of the underlying pathophysiology. Our findings are atypical for acute respiratory distress syndrome or thrombotic vascular disease and point to a possible central role for previously underappreciated pulmonary vascular shunting. More detailed assessments of vascular and perfusion changes in patients with COVID-19 are urgently needed.

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