Rethinking COVID-19 ‘pneumonia’ – is this primarily a vaso-occlusive disease, and can early anticoagulation save the ventilator famine?

Ting-Ting Low1,* Robin Cherian1,* Shir Lynn Lim1, Bharatendu Chandra2,*, Moon Ley Tung3, Shoban Krishna Kumar4, Priscillia Lye4, Amanda Chin Xin Yi4, Lynette Teo5 and Edgar Lik-Wui Tay1

1Department of Cardiology, National University Heart Centre Singapore, Singapore; 2Division of Neurology, National University Hospital, Singapore; 3Department of Haematology-Oncology, National University Cancer Institute, Singapore; 4Department of Medicine, National University Hospital, Singapore; 5Department of Diagnostic Imaging, National University Hospital, Singapore

Pulmonary Circulation 2020; 10(3) 1–3
DOI: 10.1177/2045894020931702

Preamble
As the COVID-19 pandemic rampages around the globe, it remains an enigma as to how a fraction of those infected can turn critically ill with severe hypoxemia – the scale of this problem so massive that hospitals in seriously affected cities see their ventilator capacity overwhelmed. As of 25 April 2020, there are approximately 2.6 million infections with more than 180,000 deaths worldwide.1 The main driver of mortality and morbidity with COVID-19 has been the acute respiratory syndrome that occurs in 12–32% of patients2–4 after the initial upper respiratory tract symptoms. While it is widely suspected that an abnormal host response such as a ‘cytokine storm’ is the driving force in those precariously ill,5 there are peculiarities in radiological findings and ventilator mechanics that are atypical of the usual viral pneumonia and acute respiratory distress syndrome (ARDS).

Increasingly, published data and anecdotal observations indicate that the pathogenesis may lie primarily in the pulmonary vasculature with the newly observed tendency for thrombi formation.

Early radiological findings more consistent with diffuse pulmonary microthrombi than airway or interstitial disease

The computed tomography (CT) features of the lungs in early-stage COVID-19 (0–4 days from onset of symptoms) are characterised by ground glass opacities (GGOs) distributed in the peripheral and posterior parts of the lungs.6 The significance of GGO is generally understood to be non-specific and merely implies interstitial edema and/or early alveolar exudate. Disappearance of these lesions after atomised thrombolytic suggests that these opacities are likely due to thrombosis rather than infection or inflammation,7 and these GGOs may well be a premonitory sign of pulmonary infarction. Anti-phospholipid antibody syndrome with diffuse pulmonary microvascular thrombosis presents with the same picture on high resolution CT scan (HRCT).8

The progressive stage of COVID-19 on CT (5–8 days from onset of symptoms) is demonstrated by bilateral multi-lobe distribution with diffuse GGO, crazy-paving pattern and wedge-shaped consolidation most aggravated at the lung peripheries. The lack of contiguous spread with central sparing along the proximal airways is not characteristic of a usual viral pneumonia with airway spread or diffuse alveolar damage. The consolidative changes seen on CT are possibly progressive ‘pulmonary infarcts’; however, neither CT pulmonary angiogram nor HRCT are sensitive or specific in diagnosing early microvascular thrombosis in the lung and do not help with primary cause determination. A dual energy CT perfusion scan9 of the lungs early in the course of illness may give the answer instead, as it allows qualitative assessment of perfusion defects at the microvascular level.

Pulmonary microthrombi likely secondary to thrombo-inflammatory early in the disease

Coagulation abnormalities seen in the early phase of COVID-19 illness do not correspond to a typical septic
coagulopathy or disseminated intravascular coagulation.\textsuperscript{5,10} In the early course of COVID-19 illness, elevated D-dimer and fibrinogen level indicate the presence of localised fibrin clots, while the absence of thrombocytopenia with normal clotting times argues against a consumptive coagulopathy. Direct endothelial cell infection and endothelitis in COVID-19 can contribute to impaired microcirculatory function in vascular beds\textsuperscript{11} and set the milieu for the occurrence of a prothrombotic state early.

Autopsies in COVID-19 patients are not widely performed, given the infection control precautions required to be undertaken within forensic departments with the need for negative-pressure autopsy suites or isolation rooms. In small series of autopsies, there were notable CD4\textsuperscript{+} aggregates around thrombosed small vessels, suggesting thrombotic microangiopathy restricted to the lungs\textsuperscript{12}; fibrinous thrombi demonstrated in pulmonary microvasculature suggest a hypercoagulable state,\textsuperscript{13,14} and there was also recently documented generalised thrombotic microvascular injury mediated by intense complement activation.\textsuperscript{15}

**Dissociation between respiratory mechanics and severe hypoxemia suggests an early pulmonary perfusion problem**

While severe COVID-19 pneumonia can tick off the checklist for the ARDS criteria,\textsuperscript{16} intensivists have observed a dissociation between severe hypoxemia and relatively well-preserved lung mechanics.\textsuperscript{17} Unlike the usual ARDS phenotype, COVID-19 patients intubated for severe hypoxemia had high respiratory compliance and tidal volumes. In other words, there is still normal alveolar ventilation at the outset, and diffuse alveolar damage is unlikely the inciting event for respiratory failure.

The observed lung mechanics mirror that of acute pulmonary embolism\textsuperscript{16}; furthermore, the improvement in oxygenation with prone positioning described in COVID-19 patients is in keeping with regional perfusion defects.\textsuperscript{18}

**Clinical trajectory in severe COVID-19 ‘pneumonia’ reflects pulmonary vaso-occlusive disease**

COVID-19 patients who are just found to be dyspnoeic or hypoxic can deteriorate quickly. Due to large flow reserve capacity, more than 40\% of the pulmonary vascular bed may be occluded by the time hypoxemia occur,\textsuperscript{19} and the risk of cardiorespiratory collapse becomes imminent. Additionally, the paucity of dyspnea despite profound hypoxemia in COVID-19 makes it difficult to identify a high-risk patient clinically. This clinical picture mirrors patients with peripheral subsegmental pulmonary emboli who show minimal or no symptoms that precludes early diagnosis,\textsuperscript{20} but risk rapid decline especially with endotracheal intubation.

It is plausible that a large number of ‘clinically silent’ pulmonary microvascular thrombosis occurs early in this disease, which goes undetected in routine clotting time studies as well as routine radiology imaging (such as chest radiograph or CT). If left untreated, diffuse pulmonary microthrombi can result in a cascade of thrombo-inflammatory process leading to worsening of the hypercoagulable state, causing rapid clinical deterioration in the patient. This phenomenon is observed in many intensive care patients, and the presence of thromboembolism with significant consumptive coagulopathy should already signify a very advanced stage of this disease process.\textsuperscript{21}

**Major implications of this hypothesis and a silver lining for early intervention**

Despite the onslaught of patients who desperately need treatment, there is currently no proven therapy for COVID-19. The prediction of trajectory of illness from symptom onset is difficult, and decline to respiratory failure is often abrupt. It is increasingly recognised that severe COVID-19 has a ‘vascular’ component to it, and experts have weighed in on the ventilatory management in the critically ill.

Establishing pulmonary microvascular thrombosis as the inciting event for COVID-19 respiratory distress syndrome offers a possibility for early anticoagulation to avert the ventilator famine. Performing dual energy CT perfusion scan of the lungs early in the course of illness before the development of peripheral consolidative changes may be elucidating. High D-dimer levels associated with poor outcomes in COVID-19 may be related to the undetected presence of pulmonary microthrombi and can be utilised to risk stratify patients for anticoagulation.

If pulmonary microvascular thrombosis is indeed the primary driver of severe COVID-19, it is conceivable that early diagnosis and timely management could alter the natural course of the disease. This will greatly alleviate the staggering medical, social and economic burden of COVID-19 worldwide.

**Conflict of interest**

The author(s) declare that there is no conflict of interest.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**ORCID iDs**

Ting-Ting Low \(\text{https://orcid.org/0000-0001-5359-9860}\)
Robin Cherian \(\text{https://orcid.org/0000-0003-1563-4340}\)
Bharatendu Chandra \(\text{https://orcid.org/0000-0002-6777-4137}\)

**References**

1. World Health Organization. Coronavirus disease (COVID-2019) situation reports, www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed 13 April 2020).
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.

3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–513.

4. Remuzzi A and Remuzzi G. COVID-19 and Italy: what next? Lancet 2020; 395: 1225–1228.

5. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020; 395: 1517–1520.

6. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 2020; 295: 715–721.

7. Wu Y, Wang T, Guo C, et al. Plasminogen improves lung lesions and hypoxemia in patients with COVID-19. QJM Published online Apr 10 2020; DOI: 10.1093/qjmed/hcaa121.

8. Maggiorini M, Knoblauch A, Schneider J, et al. Diffuse microvascular pulmonary thrombosis associated with primary antiphospholipid antibody syndrome. Eur Respir J 1997; 10: 727.

9. Renard B, Remy-Jardin M, Santangelo T, et al. Dual-energy CT angiography of chronic thromboembolic disease: can it help recognize links between the severity of pulmonary arterial obstruction and perfusion defects? Eur J Radiol 2011; 79: 467–472.

10. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18: 1023–1026.

11. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395(10234): 1417–1418.

12. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. MedRxiv 2020; DOI: https://doi.org/10.1101/2020.04.06.20050575.

13. Dolhnikoff M, Duarte-Neto AN, Rada M, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost 2020; DOI: 10.1111/JTH.14844.

14. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol 2020; 1–8.

15. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases [published online ahead of print, 2020 Apr 15]. Transl Res 2020; S1931–5244(20)30070-0.

16. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307: 2526–2533.

17.Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020; DOI: https://doi.org/10.1007/s00134-020-06033-2.

18. Dunham-Snary KJ, Wu D, Sykes EA, et al. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest 2017; 151: 181–192.

19. Burrowes KS, Clark AR and Tawhai MH. Blood flow redistribution and ventilation-perfusion mismatch during embolic pulmonary arterial occlusion. Pulm Circ 2011; 1: 365–376.

20. Yoo HH, Queluz TH and El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. Cochrane Database Syst Rev 2016; 1: CD010222.

21. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020; DOI:10.1001/jamainternmed.2020.0994.