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COMMENTARY

The vascular nature of COVID-19

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ABSTRACT

A potential link between mortality, D-dimer values and a prothrombotic syndrome has been reported in COVID-19 patients. The National Institute for Public Health of the Netherlands published a report for guidance on diagnosis, prevention and treatment of thromboembolic complications in COVID-19 with a new vascular disease concept. The analysis of all available current medical, laboratory and imaging data on COVID-19 confirms that symptoms and diagnostic tests can not be explained by impaired pulmonary ventilation. Further imaging and pathological investigations confirm that the COVID-19 syndrome is explained by perfusion disturbances first in the lung, but consecutively in all organs of the body. Damage of the microvasculature by SARS 1 and SARS 2 (COVID-19) viruses causes microthrombotic changes in the pulmonary capillaries and organs leading to macrothrombosis and emboli. Therefore anticoagulant prophylaxis, close lab and CT imaging monitoring and early anticoagulant therapy are indicated.

In their retrospective study, Fei Zhou et al reported on the clinical course and risk factors of adult patients in Wuhan (China) suffering from the COVID-19 viral infection¹. This study has been of high importance since it presented the first clinical outcome data in the COVID-19 pandemic. A plethora of publications on COVID-19 emerged hand in hand with the spread of the disease, mostly explaining the disease from a monodisciplinary perspective. The Wuhan data were confirmed by reports from European and American publications, but there remained a disorientation on the explanation of the COVID-19 syndrome. The general opinion was and still is that COVID-19 is a primary pulmonary infection affecting the respiratory tract complicated by classic deep vein thrombosis and pulmonary embolism.²⁻⁴ The multidisciplinary report that was published on the ninth of April by the National Institute for Public Health of the Netherlands postulated that the "ARDS" syndrome in COVID-19 was not simply caused by impaired ventilation but primarily by impaired pulmonary perfusion as a result of microvascular obstruction.⁵

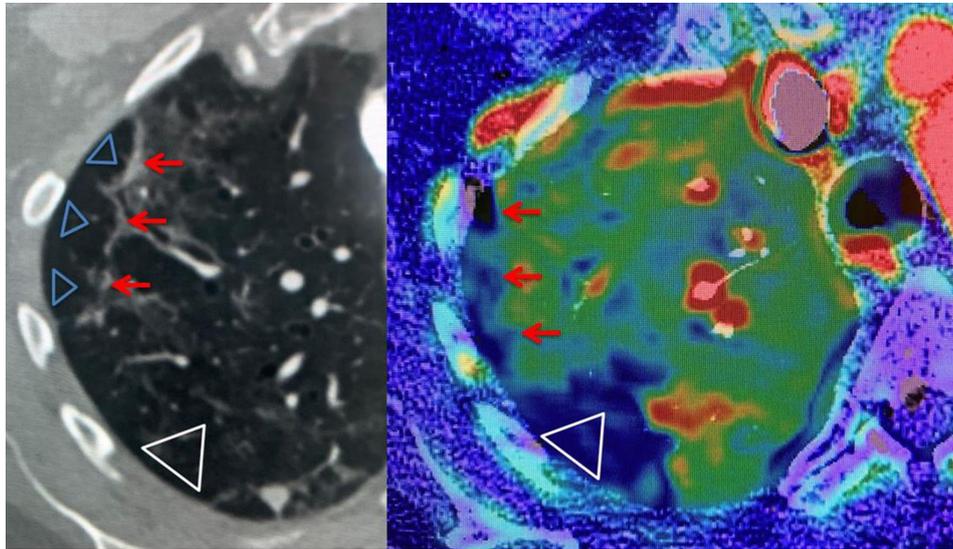
It was stated that the viral infection invaded the endothelium of the systemic vascular system damaging the Angiotensin Converting Enzyme two (ACE2) receptors thereby releasing angiotensin II and triggering microthrombus

development and inflammation at the same moment.⁶ ACE2 is present in most organs: ACE2 is attached to the cell membrane of mainly arterial and venous endothelial cells, lung type II alveolar cells, enterocytes of the small intestine, and arterial smooth muscle cells in most organs.

Therefore, the initial pulmonary symptoms can be explained by a (pro)thrombotic syndrome with endotheliitis at the alveolar and capillary venous level causing diffuse alveolar damage. If thrombusformation is not stopped by timely treatment, the disease, in combination with other risk factors, such as immobilization, will develop to arterial and venous macrothrombosis and embolism. This explains the very high percentage of patients with arterial pulmonary thrombi in late stage COVID-19 disease in combination with low percentages of DVT in the same patient population.⁷

This COVID-19 disease concept is supported by the Wuhan data which show strongly increasing D-dimer levels in *non-survivor* patients. All survivors, which are the vast majority, have normal D-dimer levels.¹ Furthermore, publications from all over the world confirmed the macrothrombosis and pulmonary embolism in the late and end stage of the disease development. In hospitalized patients, steep

Figure 1. Chest CT perfusion angiography in COVID-19. A COVID-19 positive tested female of 54 years, presented with fever and dry cough since 10 days, with clinical suspicion of pulmonary embolism. (a) Chest baseline CT of the right upper lobe with subpleural bands of organizing pneumonia (red arrows), surrounded by small ground glass opacities (GGOs). (b): CT perfusion angiography image shows multiple small subpleural perfusion defects (red arrows) and a larger perfusion defect dorsal in the *normal ventilated* right upper lobe (Δ 1a), due to microvascular obstruction (Δ 1b). CT angiography showed no pulmonary emboli in the right pulmonary upper lobe resulting in a perfusion/ventilation mismatch. Scan parameters: Conventional Dynamic Perfusion CT, Somatom Drive, Siemens; Scan volume 8,4 cm (aorta arch – left atrium); 1mm recon; Dual input lung perfusion 4D, Vitrea, Vital, Canon; (Figure courtesy of Department of Radiology, Haaglanden Medical Centre, The Hague, the Netherlands.)



elevated D-dimer values always have an underlying (secondary) cause, of which 50% of cases proved to be pulmonary emboli (PE) and deep vein thrombosis (DVT).⁸ These findings are also applicable to the COVID-19 disease development. In the meantime, the ARDS syndrome in COVID-19 as such is questioned in several publications referring to perfusion disturbances as the explanation of the early presentation of the COVID-19 symptoms.⁹ The Public Health Report of the Netherlands provides a proof of this concept by a patient example of multiple pulmonary perfusion defects, detected with CT Perfusion Angiography in a very early stage of the disease even before D-dimer elevation, and without demonstrable pulmonary embolism (Figure 1). After the publication of this report, several post-mortem studies have proven the presence of systemic micro- and macrovascular thrombosis and diffuse alveolar damage.¹⁰ One post-mortem study compared influenza and COVID-19 pneumonia and observed micro- and macrovascular thrombosis nine times more frequently in COVID-19.¹¹ Microvascular thrombosis in pulmonary veins and in almost all other organs have been confirmed in all post-mortem studies so far. Several post-mortem studies report vascular endotheliitis as a complication of COVID-19.¹² Notably post-mortem observations do not reveal secondary bacterial or fungal infection.¹³

The radiological features of the lungs at disease onset are bilateral ground glass opacities (GGO's) and vessel enlargement in almost all cases (>90%).¹⁴ These findings can be explained by the (sub)acute flow redistribution as a result from the microvascular obstruction and pulmonary thrombosis, expressing interstitial edema and hyperaemia circumventing the thrombosed, normal ventilated pulmonary lobules. This matches with post-mortem

results where transudate is found as a result of the vascular obstruction and congestion and not exudate fluid as one would expect in pulmonary inflammation.¹⁵

All this evidence proofs the vascular impact of COVID-19 causing an endothelial vasculitis and microvascular thrombosis at the moment it attacks the ACE2 receptor of the vessels resulting in a process of thrombo-inflammation in the disease onset and therefore cannot be regarded as just a complication of COVID-19. Studies have shown that anticoagulants have a substantial positive impact on outcomes in COVID-19.^{3,16}

Direct contrast CT visualization of thrombi in the post-capillary pulmonary veins remains a major challenge as it is beyond CT visualization thresholds with current technology. As a consequence *pulmonary thrombosis is at this dark side of the moon*. Since the thrombotic complications are the cause of death in many patients with COVID-19, (micro)thrombus development should be monitored with D-dimer testing as recommended in the national report. This test has a 99% negative predictive value for thrombosis and PE and also yields prognostic information for COVID-19 disease. CT perfusion angiography would be a powerful tool to demonstrate pulmonary perfusion defects, but is an advanced CT technique and still not routinely available. Dual energy CT, which is also promoted, reflects only the contrast enhanced blood pool in steady state without a temporal component.¹⁷ Non-contrast CT can detect the very early signs of pulmonary microvascular thrombosis by the typical presentation of GGOs and vessel enlargements even before the PCR test becomes positive. In the vast majority of these patients, D-dimer levels are <1000 ng/ml¹. They can be sent home safely as soon as symptoms allow. In those with plasma D-dimer

>1000 ng/ml, preventive and therapeutic anticoagulation should start immediately and D-dimer monitoring is indicated. Most hospitalized patients with COVID-19 with rapid breathing, dry cough, and hypoxaemia will positively respond to supplemental oxygen. In the later stage of the disease contrast-enhanced CT can easily detect pulmonary arterial thrombus and PE, which is diagnosed in a large number of patients. PE is known as the silent killer, but one prominent (often unrecognized) symptom in 35% of patients stands out: *sudden onset of dyspnea*. This symptom is extensively reported by public health authorities worldwide as part of the COVID-19 syndrome and reflects symptoms in the second critical phase of the disease development. Although virtually in all hospitalized COVID-19 patients, the prothrombin times (PT) are shortened within the normal range, in the second phase of the disease bleeding complications can still occur from disseminated intravascular coagulation (DIC). For all intensive care patients with proven COVID-19, D-dimer could be the dichotomous test for those at increased risk of thrombotic complications versus those that have a good prognosis. Finally, one should keep in mind that the vast majority of COVID-19 infected people recover without any significant symptoms and will never be hospitalized.

In summary, COVID-19 viral infection induces a complete new vascular disease syndrome, which initiates a viral attack on the ACE2 receptors of the microvasculature system, resulting in two distinct processes: microvascular thrombosis and inflammation of the endothelium. From all available autopsy evidence, it becomes clear that the microthrombotic process is the most prominent primary feature, affecting the lungs and other organs. Microvascular thrombosis in the lungs causes ventilation-perfusion mismatch and results in hypoxaemia. Secondary, with systemic progression of macrothrombosis (due to a combination of vascular inflammation and existing risk factors), pulmonary embolism will develop. The inflammatory component further enhances the thrombotic process in all organs. From the current evidence on therapeutic intervention, anticoagulant therapy and anti-inflammatory treatment (low dose) are the most effective in terms of survival benefit and IC occupancy. CT imaging in combination with D-dimer values provides biomarkers to diagnose and monitor these (pro)thrombotic and embolic processes of COVID-19 disease.

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