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Short Report
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# Is SARS-Cov-2 an Inflammatory Thrombotic Disorder?

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## Short Report

Preliminary interesting results observed in patients Covid-19 treated with dipyridamole underlined the potential role of thrombosis in the pathophysiology [1]. Beside the use of dipyridamole as an anti-aggregating agent in coronary syndrome or cerebral vascular complications, it was tested in Thrombotic Thrombocytopenic Purpura (TTP), a disease due to infections by several agents which affects mostly children. The classical and efficient treatment was plasma exchange.

The clinical trial in TTP with dipyridamole can never go to its end since the number of patients was limited. High dose of dipyridamole was reported to be effective in a patient with TTP [2]. The symptoms observed in patients with multi-organ failure have at least in common the renal insufficiency and elevation of thrombotic biological markers. High levels of D-dimers and multiple organ failure were observed during infection in children with TTP, in adults with Macrophage Activation Syndrome (MAS). Several aspects of the thrombotic process are different in SARS-CoV-2. In TPP the kidney was mostly affected, in MAS the intravascular coagulation is more disseminated. Activation of endothelial cells induced cytokines production IL-6, MCP-1 and tissue factor expression leading to inflammation and thrombosis (Figure 1) [3]. D-dimers elevation and augmented IL-6 are associated to a high level of mortality consistent with vascular endothelial cell dysfunction. Angiotensin converting Enzyme receptors present on endothelial cell may facilitate the infection of endothelial cells, apoptosis and thrombosis [4]. This phenomenon may partly explain the encephalopathy in Covid-19 [3].

Pyrimido-pyrimidine compounds include dipyridamole and a number of its analogues. They inhibit platelet aggregation and the platelet release reaction induced by most aggregating agents. In addition dipyridamole inhibits platelet adhesion to collagen and to the sub endothelial structures. In experimental animals, dipyridamole can be administrated in doses which interfere with hemostatic plug formation and prolong the bleeding time. In venous thrombosis in patients undergoing hip surgery, dipyridamole was ineffective.

In patients with Covid-19 the apparent beneficial effect of dipyridamole is surprising since platelet count is slightly modified at variance with the TTP and the macrophage activation syndrome. The evidence of vascular inflammatory process and thrombosis are clear. These phenomena may be explained by NADPH oxidase stimulation and consequently an alteration of gene expression of molecules [5]. Vascular endothelial cells can be a direct target for SARS-CoV-2 associated to leukocyte recruitment and a possible cross-talk between these two types of cells via cytokines, reactive oxygen species, and activation of specific receptors.

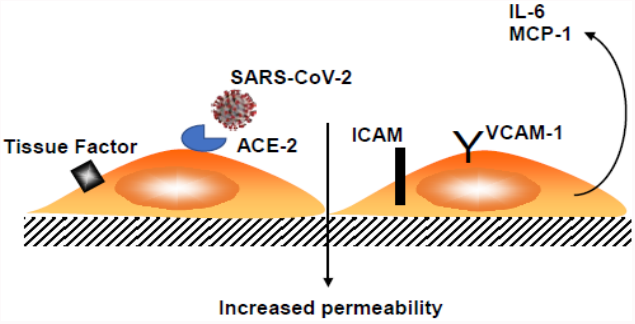


**Figure 1:** Activation and dysfunction of endothelial cells induced by SARS-CoV-2: The binding of SARS-CoV-2 to Angiotensin Converting Enzyme-2 (ACE-2) receptor induced an activation of endothelial cells leading to Tissue Factor production, Interleukin-6 (IL-6) and Monocyte Chemoattractant Protein-1 (MCP-1) release, expression of Intercellular Cell Adhesion Molecule (ICAM) and Vascular Cell Adhesion Molecule-1 (VCAM-1), increase in vascular permeability.

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Hydroxychloroquine was reported to be a possible treatment of Covid-19. The Chloroquine has been used extensively as anti malarial agents but they also have some anti-inflammatory properties. In prospective studies in which venous thrombosis has been diagnosed clinically by venography or by $^{125}$I-fibrinogen leg scanning, hydroxychloroquine has been found to prevent venous thrombosis. Hydroxychloroquine in doses of 600 mg daily produces a significant reduction in the incidence of deep vein thrombosis and pulmonary embolism [6]; however it could produce side effects on heart functions.

ACE receptors and other SARS-CoV-2 receptors are present on endothelial cells, mostly on lung vessel endothelial cells. This may explain why pneumonia is a dominant symptom and at variance with other intravascular coagulation platelet number is slightly reduced.

The consequences well demonstrated are inflammation and thrombosis. The treatment by heparin family molecules and drugs which block cytokine activators of endothelial cells seems to be logical and should probably be applied in the first part of the disease at least before alveolar destruction and pulmonary vessel thrombosis.

Anti-aggregating agents may be beneficial by an anti-thrombotic activity not directly linked to platelets. Heparin anticoagulation was used in a majority of patients as prevention or treatment of thrombosis. The association of anti platelet drugs will increase the risk of hemorrhage.

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