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COVID-19 May Predispose to Thrombosis by Affecting Both Vascular Endothelium and Platelets

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The target of the novel coronavirus disease 19 (COVID-19) is not only lung tissue but also vascular endothelium since vascular endothelium has angiotensin-converting enzyme 2 (ACE2)-like lung tissue. Vascular endothelium has many functions and it is the only place where the von Willebrand factor (VWF) is stored. COVID-19 often causes thrombosis attacks during its infection. It is known that the angiotensin II level increases during infection of the virus.

Angiotensin II is one of the strongest stimulants of Na^+/H^+ exchanger (NHE). Elevated lactate levels and hypoxia cause H^+ ions to increase and move into the cell. It has been claimed that angiotensin II level and H^+ ion increase make NHE continuous and overactive during virus infection.[1] NHE1 isoform is found in both vascular endothelium and platelets. Activation of NHE plays a key role in the development of thrombosis. The NHE pumps $3Na^+$ inward the cell and $2H^+$ out of the cell. Simultaneous to the activation of this pump, a rapid accumulation of Ca^{2+} occurs inward the cell.[1] Alkalization of the intracellular pH by activation of NHE in the vascular endothelium leads to the VWF release. The VWF release from the endothelium doubled after 10 minutes after the intracellular pH was alkalized by NHE activation after acid loading.[2] Activation of the NHE pump not only causes accumulation of Ca^{2+} into the cell but also activates protein kinase C.[2] Both intracellular Ca^{2+} flow and protein kinase C activation cause VWF release from the endothelium. Unlike NHE activation, NHE inhibition decreases VWF release by inhibiting endothelial activation.[2] While NHE is pumping H^+ ion out of the cell, Ca^{2+} moves into the cell simultaneously. This ion transfer increases oxidative stress and causes endothelial dysfunction. Inhibition of NHE with amiloride prevents endothelial dysfunction.

Healthy endothelial cells promote anticoagulant properties and prevent platelet activation and aggregation. In endothelial dysfunction, adhesion of platelets to endothelium increases. The VWF multimers align along the surface of the endothelium or damaged vein. Platelet GpIbα parts interact with the VWF-A1 domains, and platelets adhere to the surface of endothelium and damaged vein. Platelets also have NHE1 isoform, and NHE activation in platelets also shows a procoagulant effect. Angiotensin II activates NHE1 in platelets. Activation of NHE in platelets leads to the flow of Na^+ into platelets.[3] During the movement of Na^+ inward of platelet, the platelet membrane structure also deteriorates, and fibrinogen receptors in the platelet membrane are activated.[3] Since Na moves into platelets with water, platelets swell.[3] The swelling of platelets causes them to appear in petite sizes.[3] The procoagulant platelet numbers increase by desmopressin stimulation.[3]

In conclusion, angiotensin II levels are increased with ACE2 blocking by COVID-19. Angiotensin II stimulation and local stimuli such as H^+ ion and hypoxia activate NHE in both vascular endothelium and platelets. COVID-19 can lead to thrombosis by causing NHE activation.

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