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# Heparan sulfate consumption as a potential mechanism of intra-cardiac thrombosis in SARS-CoV-2 infection

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Cardiac injury occurs in up to 36% of hospitalized patients with COVID-19.[1] Exact mechanism of cardiac injury in COVID-19 is not well understood, but may relate to direct cardiomyocyte damage, coronary plaque destabilization, cytokine inflammatory response, and intracoronary microthrombi formation. Lindner et al.[2] in an autopsy study identified SARS-CoV-2 RNA in the myocardium in 24 of 39 autopsy cases. However, none of the 39 patients had myocarditis. Plasma pro-inflammatory cytokine levels were increased in 16 patients, suggesting cytokine response as a plausible cause of cardiac injury in COVID-19. Early reports identified ACE2 as a receptor for the SARS-CoV-2. Clausen et al.[3] have recently identified heparan sulfate as a co-receptor for ACE2, whereby SARS-CoV-2 binds to heparan sulfate, a negatively charged polymer, through a positively charged site adjacent to the ACE2 binding domain. Heparan sulfate is ubiquitously expressed in mammalian tissues, and ACE2 is broadly expressed in the arterial, capillary, and venous endothelial cells. Heparan sulfate also interacts with antithrombin, which subsequently undergoes conformation change, resulting in the generation of the active form of antithrombin. The active form of antithrombin inhibits the procoagulant factors Xa and thrombin (IIa) (Fig. 1). Additionally, Gue et al.[4] suggested that reduction in ACE2 activity may increase vascular permeability resulting in increased expression of tissue factor in subendothelial cells, leucocytes, and platelets with subsequent activation of coagulation and thrombosis.

As SARS-CoV-2 binds heparan sulfate and ACE2 for cellular entry, it is possible that the high expression of ACE2 in the heart would facilitate an interaction between SARS-CoV-2 and heparan sulfate, leading to heparan sulfate consumption. A lower level of heparan sulfate would lead to a reduction in antithrombin activation creating a hypercoagulable state. Heparan sulfate also mediates antithrombin's anti-inflammatory activity.[5] Loss of antithrombin's anti-inflammatory activity can potentially lead to endothelialitis and subsequent endothelial injury and intra-cardiac thrombus formation.

We believe that heparan sulfate consumption during SARS-CoV-2 cellular entry might play a role in the thrombotic events associated with COVID-19 infection.

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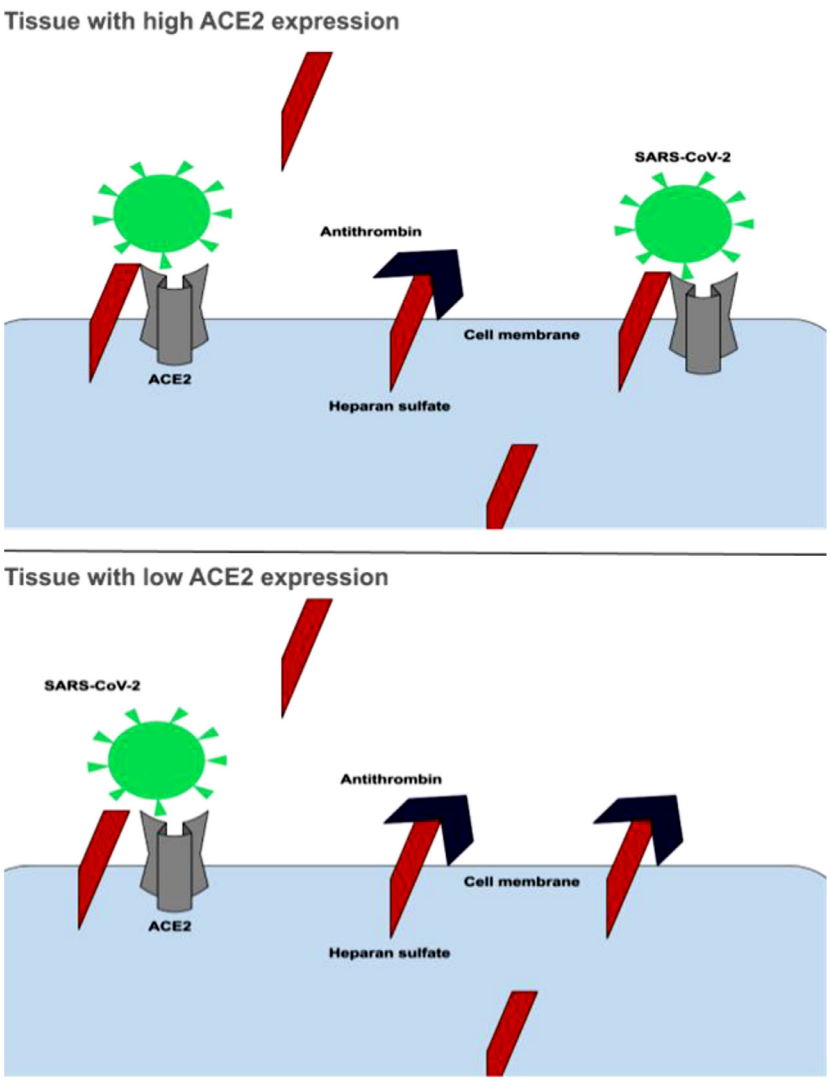


**Fig. 1.** Hypothesized mechanism for thrombotic events in COVID-19.

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