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LETTER TO THE EDITOR

Letter in response to: Coagulation markers are independent predictors of increased oxygen requirements and thrombosis in COVID-19

We read with interest the recent publication by Rauche et al and congratulate them on highlighting the potentially significant role von Willebrand factor (VWF) may play in the progression and prognosis of COVID-19. Since SARS-Cov2 first presented there has been an increasing recognition that the disease may trigger a widespread endotheliopathy. This fact could help to explain the highly varied presentation of patients with COVID-19 from bowel ischemia to large vessel occlusion causing strokes in addition to the more common presentation of respiratory symptoms. At the same time there has been an increased understanding that the infection may result in microthrombosis as well as macrothrombosis both on the arterial and venous side of the circulation. Contrast enhanced ultrasound was recently used to identify microthrombi and wedge-shaped perfusion defects in vivo in the pulmonary, renal, and gastrointestinal beds. Routine imaging methods, such as computed tomography (CT) and CT angiography, do not have the spatial or contrast resolution to detect microvascular thrombosis and therefore, the demonstration of perfusion defects in vivo has been delayed. Post mortem studies have also shown microthrombosis within the lungs confirming the in vivo imaging findings. In the study of Carsana et al, microthrombi, in vessels < 1mm in diameter, were seen in 87% of cases. A further case series of COVID-19 pulmonary autopsies revealed that, alongside diffuse alveolar damage, numerous localized platelet-rich microthrombi, and foci of hemorrhage were present in the lungs. The authors posited a pulmonary-localised thrombotic microangiopathy as key to the pathogenesis of COVID-19 with others also suggesting the micro-thrombosis is a critical driver in the disease process.

Von Willebrand factor is synthesized only in megakaryocytes and endothelial cells (ECs). The vast majority of VWF found in the plasma is derived from the VWF synthesized within the ECs, where it is stored within the Weibel-Palade bodies (WPB). Although restricted to ECs there are differences in the synthesis of VWF within the different vascular beds of the body with the small vessels of the lung and brain expressing higher levels of VWF than similar sized vessels of the liver or kidney and higher levels in venous rather than arterial ECs. A major portion of the VWF stored in the WPBs of endothelial cells is made up of ultra-large VWF (ULVWF). These larger multimers are more adhesive than the smaller multimers in the circulation and upon secretion ULVWF can spontaneously bind...
platelets and cause occlusion of small vessels. The secreted VWF, which partly enters the circulation and partly binds to the endothelium, is sensitive to shear stress. This shear stress unfolds the VWF and exposes sites for platelet binding and self-association as well as for cleavage via the enzyme ADAMTS13. The secreted VWF, which partly enters the circulation and partly binds to the endothelium, is sensitive to shear stress. This shear stress unfolds the VWF and exposes sites for platelet binding and self-association as well as for cleavage via the enzyme ADAMTS13. It has previously been shown these VWF molecules can self-associate into long “strings” in the direction of flow, both arterial and venous, that bind to platelets and are adherent to the endothelium.\(^8\)\(^9\) The ULVWF multimers released from the WPBs unfold at lower levels of shear stress and therefore may represent the initiating molecules for this self-assembly process, which leads to hyper-adhesive strings capturing platelets. Preventing the binding of platelets to ULVWF may represent an attractive site to prevent microthrombosis formation. Inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha, as well as hypoxia, can trigger the exocytosis of WPBs with release of their contents while IL-6 can inhibit the cleavage of ULVWF–platelet strings.\(^10\) Furthermore, the synthesis of ADAMTS13, at least in cultured cells, is dramatically inhibited by a variety of cytokines including IL-6 and TNF-alpha.\(^11\) This suggests that hypoxia, the cytokine storm, and particularly IL-6, may help to propagate the microthrombosis.

One of the most interesting findings of the published work was that the 10 patients presenting with normal VWF levels did not require admission or treatment with oxygen and we believe that this supports the concept that VWF plays a critical role in the pathogenesis. Furthermore, it is possible that VWF levels and the VWF:factor VIII (FVIII) ratio could act as biomarkers for determining which patients are likely to progress as well as those that are responding to treatment. The recent finding of ABO blood type and disease severity also points to a potential link with VWF with those patients with type O blood group being at lowest risk and those with type A being at highest risk.\(^12\) Patients with type O have lower levels of VWF compared to those with non-O blood group and those with non-O blood group are at higher risk of arterial thromboembolic disease such as ischemic heart disease and peripheral vascular disease. Although the exact nature of the interaction remains unknown it has been suggested that ABO blood group determinants may be important in influencing the susceptibility of plasma VWF to proteolysis by ADAMTS13.\(^13\) Therefore, it is possible patients more susceptible to severe disease are already predisposed to thromboembolic diseases and that the sudden surge in VWF, particularly ULVWF, triggered by a widespread endotheliopathy overwhelms the body’s innate ability to break down VWF via ADAMTS13. Further evidence for this comes from the recent work of Ladikou et al.,\(^15\) who are the first to show a marked drop in circulating ADAMTS13 levels (49.7% of normal) with the authors stating “we speculate that excess release of VWF seen in COVID-19...
patients leads to depletion of ADAMTS13 and contributes to the prothrombotic state."

If thromboembolic complications play a significant role in the pathogenesis of the disease as it is now widely accepted, then targeting this seems a natural course of action. In the recent propensity score-matched study by Tremblay et al, there was no difference in the outcome of patients who were on prior anti-platelet or anti-coagulant medication compared to those who were not. This may suggest that standard approaches to anti-aggregation and anti-coagulation are insufficient. This could be explained by the fact that the ULVWF strings mentioned earlier are sufficient to occlude vessels alone and this will not be inhibited by standard treatments.

Taking all of this into account we believe that there is now compelling evidence for a critical role of VWF in COVID-19. Rather than merely representing a biomarker we believe it plays a pivotal role in the pathogenesis and prognosis of the disease. Targeting VWF, particularly early in the disease course, through agents such as caplacizumab or anifabatide, both of which inhibit binding of platelets to the VWF at the glycoprotein IX-Ib receptor, presents an attractive opportunity that is yet to be explored (Figure 1).

CONFLICTS OF INTEREST
PB, DH, and OJ have approached Sanofi to trial caplacizumab in COVID-positive patients. MM, GC, OS, and LM have no conflicts to disclose.

AUTHOR CONTRIBUTIONS
PB: originator of concept, manuscript drafting, editing. MM, GC, OS, LM, DH: critical review of manuscript, editing. OJ: guarantor.

KEYWORDS
COVID 19, anifabatide, caplacizumab, endotheliopathy, microthrombosis

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