Editorial

In Vitro Evidence for the Role of Cytokine Storm in the Generation of Stent Thrombosis in COVID-19 Patients

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COVID-19 is a prothrombotic disease that enhances the risk for adverse complications, including stent thrombosis and mortality, in patients with acute coronary syndrome (ACS) [1–4]. COVID-19 is characterized by markedly elevated systemic levels of inflammatory cytokines [interleukin (IL-6 and tumor necrosis factor (TNF)-α)], fibrinogen, and d-dimer and a resultant hypercoagulable state [5,6]. Thus, ACS, a prothrombotic disease, is further aggravated by COVID-19. Several studies, including case reports, demonstrated higher rates of stent thrombosis and hospital mortality in patients with COVID-19 who were stented for ST-segment elevation myocardial infarction (STEMI) compared to patients with STEMI without COVID-19 [2–4,7]. Moreover, a higher incidence of multiple thrombotic culprit lesions, higher thrombus grade, and a lower rate of procedural success of primary percutaneous intervention were also reported in patients with COVID-19 and STEMI compared to patients with STEMI alone [3,8]. Elevated levels of d-dimer were also associated with high thrombus burden and low myocardial blush grade among these patients [3]. These important findings support the concept that patients with COVID-19 and STEMI ideally should be treated with the least thrombogenic stent(s).

In this issue of *Cardiovascular Revascularization Medicine*, Cornelissen et al. evaluated the inflammation potential and acute thrombogenicity of different stents using a novel *in vitro* flow loop and blood from healthy volunteers spiked with high levels of IL-6 plus TNF-α to simulate the COVID-19-associated cytokine storm [9]. The markers chosen to identify stent prothrombotic potential were 2 platelet markers: 1) CD42b or glycoprotein Ib, which is expressed on the surface of platelets and involved in platelet adhesion to von Willebrand factor; and 2) CD61 or glycoprotein IIIa is a platelet surface integrin that, along with glycoprotein IIb, forms fibrinogen receptor. Myeloperoxidase (MPO), a peroxidase enzyme expressed abundantly in neutrophils, was the marker chosen to identify stent-related inflammation. The authors studied 4 stents: 1) the cobalt chromium alloy uncoated COBRA stent, 2) the COBRA coated with the fluorinated polymer, poly-bis (trifluoroethoxy) phosphazene, 3) the platinum-iridium alloy core and cobalt chromium alloy shell Resolute Onyx stent coated with the BioLinx polymer (C10, C19 and polyvinyl-pyrrolidinone polymer blend), and 4) the platinum chromium alloy Synergy stent *co*ated with the bioabsorbable polylactic-*co*-glycolic acid polymer. Blood samples from healthy volunteers on no medications was spiked with 400 pg/mL IL-6 and 100 pg/ml TNF-α to simulate cytokine storm [9–11] and circulated through stent loops at a flow rate of 35 mL/min for 60 min. These stents were later immunostained with antibodies against CD42b and CD61 to identify adhesion of platelets, and antibody against MPO to identify activated neutrophils. Platelet adhesion was least on the coated COBRA stents both in the presence and absence of simulated cytokine storm and was lower on the Resolute Onyx than the Synergy stent in the absence of cytokine storm. Neutrophil activation was observed in the presence of cytokine storm on all stents but was less in coated and uncoated COBRA stents and in Resolute Onyx than in synergy stents. In one autopsy specimen from a patient with severe COVID-19 and STEMI, the authors reported a high level of adhesion of inflammation cells and platelets to a cobalt-chromium (CoCr) everolimus-eluting stent that was greater than observed in 3 STEMI patients treated with the same stent.

This is the first report to investigate differences in stent thrombogenicity in the presence of cytokine storm. The available evidence from this study suggests that the fluoropolymer-coated COBRA stent was associated with the least platelet adhesion and inflammation. In preclinical studies, COBRA PzF nanocoated stents were associated with accelerated endothelialization and lower inflammation and thromboresistance, further supporting the current results of lower platelet adhesion and inflammation [12]. Thus, the current provocative *in vitro* study results indicate that the nanocoated COBRA-PzF may provide the maximum benefit of reduced thrombogenicity in COVID-19 patients. However, important limitations of this study include those associated with an *in vitro* experiment with an absence of living tissue,

notably, the absence of assessment of the contribution of endothelium, an absence of high levels of fibrinogen, which are hallmarks of COVID-19 laboratory characteristics, and the absence of platelet-inhibited blood. Whether the same findings would be observed in aspirin- and $P2Y_{12}$- receptor-inhibited blood are unknown. Nevertheless, this is a provocative first step to examine the potential for personalization of stent type in the setting of a highly prothrombotic and proinflammatory disease.

Declaration of competing interest

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