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REVIEW

Thrombotic aspects of SARS-CoV-2 infection: indications for treatment

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ABSTRACT

Several studies highlighted the importance of thrombotic complications during early phases of acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) as well as long-term complications, until responsible for the high mortality observed in SARS-CoV-2 infection. The relationship "increased thrombotic risk and COVID-19 infection" justified further researchers, especially those undergoing hospitalization for severe COVID-19 infection, presented thrombotic complications during follow-up, after hospital discharge and apparent healing. It was highlighted that SARS-CoV-2 infection mainly affects the upper airways, the access of the virus in the humans, while the complications are systemic, secondary to extensive endothelial damage, with consequent systemic activation of the immune system and of pro-thrombotic system. Recent data confirm that prophylactic antithrombotic treatment is useful in hospitalized patients, and in selected cases it is useful at high therapeutic dose.

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Recently, the World Health Organization (WHO) classified "post COVID-19 condition," present up to 10-20% of patients affected by COVID-19 infection, as state secondary to severe and global endothelial dysfunction, characterized by inflammatory state, prothrombotic state, vascular permeability and epigenetic alteration of the endothelium, involving pulmonary, coronary, cerebral, and skeletal muscle microvasculature; this syndrome is clinically characterized by fatigue, tachycardia, nonspecific dyspnea, cognitive impairment and reduced daily life quality, within 3 months after SARS-CoV-2 infection and last at least 2 months.[1, 2] Beyond acute manifestations of COVID-19 infection, this endotheliopathy is responsible for long-term symptoms and accelerated atherosclerosis.[3]

Evidence acquisition and synthesis

There is a growing body of evidence suggesting that thrombotic complications may occur not only during early phases of acute respiratory syndrome due to SARS-CoV-2 infection but also in the following weeks after hospital discharge. In study by Venturelli *et al*.,[4] conducted in large series of patients with previous COVID-19 infection (60% hospitalized and 8% admitted to

intensive care unit [ICU]), after 3 months from hospital discharge the extensive evaluation highlighted that about half of the patients presented persistent relevant symptoms (such as fatigue and unexplained dyspnea), while a third presented status defined as "not yet recovered" and lack of resumption of former functional activity. In this regard, 30% reported significant dyspnea assessed by the Modified British Medical Research Council Questionnaire (mMRC), of which one-fourth in severe form, and 16% of the patients reported reduced functional autonomy through Barthel Index Code. It is interesting that at the time of the reassessment after discharge, almost 24.2% of patients were still taking drugs prescribed during hospitalization, mostly anticoagulants, and the evaluation of blood tests showed persistence of altered values, as D-dimer (38%), LDH (22%) and PCR (7%). In this casuistry significant percentage of patients showed asymptomatic sub-segmental pulmonary embolism, suggested by persistence of higher D-dimer values.

Recent meta-analysis showed that in patients admitted in ICU the prevalence of pulmonary embolism (PE) or deep vein thrombosis (DVT) was around 25-37% in patients undergoing prophylactic anti-thrombotic therapy, and 85% in cases not treated with prophylactic therapy; while arterial thromboses or emboli were detected in 3-7% of patients, up to 35-70% in autoptic exams of patients who died from aggressive forms.[5]

It is clearly established that clinical features of COVID-19 infection are not primarily and solely related to acute lung injury characterized by diffuse alveolar damage (DAD) due to direct virus infection, also present in other conditions of acute respiratory distress syndrome (ARDS), but severe or fatal complications are justified by other conditions beyond DAD and ARDS, as well-known cytokines storm (massive increase of several proinflammatory mediators as IL-1B, IL-2, IL-6, IL-7, IL-10, IFN, IP-10, G-CSF, MIP-1A and TNF-α), systemic inflammation and diffuse intravascular coagulation as well as large-vessel thrombosis which often evolve into generalized tissue hypoxia and multisystem organ failure.[6] As regard, in large autoptic study of Bussani *et al*. conducted in patients who died of COVID-19,[7] several distinctive features were observed as cause of fatal outcomes in all cases, characterized by extensive congestion and destruction of lung architecture, occlusion of alveolar spaces (due to edema, intra-alveolar fibrin deposition of hyaline membranes, hemorrhage, and infiltration of macrophages and CD8+ lymphocytes), whereas in almost 10% there was macroscopic appearance of thrombosis of large pulmonary vessels, with multiple thrombi and less frequent extensive lobular infarction. Interestingly, these Authors did not find relevant signs of viral infection in other organs beyond lung, suggesting that while the lung damage was to be also attributed to direct damage of the virus, the systemic damage is to be mainly attributed to the systemic inflammatory response, with extensive endothelial damage and the activation of a prothrombotic process.

Thrombosis associated with COVID-19 is a complex process involving several vascular cells, including endothelial cells, platelets, monocytes and neutrophils, which contribute to the establishment of the prothrombotic state.[8] Whether the prothrombotic phenotype observed in COVID-19 patients is a combination of hypercoagulability and impaired fibrinolysis has been one of the theories of several clinical studies. Recent systematic reviews have found a decreased fibrinolytic capacity in COVID-19 patients,[9] especially in patients in ICU. To these aspects, main elements favoring thrombosis are immobilization, venous stasis, intubation, duration of hospitalization, endothelial inflammation and damage.[5]

In COVID-19 infection several coagulation abnormalities are observed in the macro- and micro-vasculature in lung as well as in several organs (heart, liver and kidney), characterized by widespread vasculitis (due to perivascular lymphocytic caps, edematous wall, endothelial cells appearing large, exfoliated and plumped, shedding into the vascular lumen, endothelial expression for markers of platelet adhesion and activation as VCAM-1, E-selectin, tissue factor), and extensive thrombotic vessels, typically in different stages of organization (infiltrated by inflammatory cells or in advanced fibrotic stage), especially in subjects admitted in intensive units.[10]

All these alterations are reflected by the thrombocytopenia, prolongation of the prothrombin time, elevation of D-dimer, and decreased fibrinogen levels observed in many patients. As regard, in large series of COVID-19 patients observed in Wuhan, D-dimer levels over 1 mg/l at admission predicted an 18-fold increase in the odds of dying before discharge.[11]

In addition, thromboembolic phenomena play an important role, in both systemic and pulmonary circulations, not solely in acutely hospitalized patients but also in less critically ill patients in non-intensive care units and ambulatory settings, suggesting angiocentric signature of COVID-19, related to in-situ thrombotic microangiopathy and alterations in the complex immune inflammatory cascade, especially in the pulmonary vascular bed. As regard, Dhawan and his research group suggested algorithm for follow-up to detect a combination of potential pulmonary vascular and pulmonary fibrotic sequelae, using perfusion imaging (rather than angiography) as a first-line imaging.[12] This opinion is also supported by frequent findings of non-specific symptoms of illness as well as those related to respiratory failure during the follow-up from COVID-19 infection. Moreover, previous casuistries on similar viral infection (as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome [MERS]), both associated with inflammatory response and thrombotic complications, have shown impaired lung diffusing capacity in about 15-40%, and reduced total lung capacity in 5-10% in patients after 6-24 months from acute ill.[13]

Persistent prothrombotic phenotype in long-term COVID-19 is characterized by several characteristics: increased D-dimer levels (at diagnosis and in long-term follow-up), variable fibrinogen concentration (high in the early stages, reduced in the long term), decreased platelet count, prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), increased plasma levels of complement markers (C5b-9, C5a, and C3a) and complement deposits split factor (especially C4d and C5b-9 complement complex).[14, 15] In addition to conventional tests of coagulation, several novel biomarkers were assessed to fix the risk of thrombosis and prognosis in COVID-19 patients, useful to risk stratification and prognostication as well as potentially guide therapy (*i.e*. vWF antigen or the ratio of vWF antigen to ADAMTS13, Serum and Urinary thromboxanes, platelet-leukocyte aggregates, soluble CD40L, soluble P-selectin).[16]

Anticoagulation therapy after COVID-19 infection

The use of anticoagulants, in particular LMWH at prophylactic dose during the acute phase of COVID-19 infections (which may be upgraded to therapeutic dose in selected patients), has been shown to significantly reduce the mortality rate. In fact, beyond well-established effect on blood-coagulation, the LMWHs have been recognized to have anti-inflammatory properties, consisting of inhibiting adhesion, chemotaxis, activation or proliferation of leukocyte, allosteric binding site on the T-cell receptor which prevents T-cell receptor activation, reduction of interferon-gamma secretion, interleukins and TNF-α. The main international guidelines suggest these recommendations regarding thrombotic risk and consequent use of anticoagulants at prophylactic or therapeutic dose.[17]

However, the usefulness of anticoagulation therapy after hospital discharge is still debated. Whereas hospitalized patients should not be routinely discharged on VTE prophylaxis therapy, after hospital discharge it may be considered to continue anticoagulation for extended VTE prophylaxis for selected patients who are at low risk for bleeding and high risk for VTE. Thus, while it may be intuitive to continue anticoagulant or antiplatelet therapies in patients previously treated for other underlying conditions, the selection of previously healthy subjects who may benefit form extended oral anticoagulation to reduce late thrombotic complications related to COVID-19 is more challenging.

The usefulness of new oral anticoagulants could also lie in anti-inflammatory and anti-viral properties beyond the anticoagulant effects, suggesting them as potential candidates in the management of COVID-19.[18] It is well known that the spike protein of SARS-CoV-2 is constituted by two subunits: S1 containing the host receptor

binding domain (against ACE2) and S2 responsible of the fusion of virus on host cell membrane, only after breakdown of the linkage between S1-S2 subunits, through proteolytic activation promoted by the host protease (including transmembrane protease serine 2-TMPRSS2), furin, and liposomal cathepsins.[19] Some studies show that human proteases, such as human FXa, can have significant action in reducing viral entry inside the human cell.[19] As regard, FXa inhibitors can potentially block the viral entry of SARS-CoV-2 into the host by ceasing the fragmentation of the spike protein in the S1 and S2 subunits,[18] or by inhibiting TMPRSS2 in a broad spectrum of infection by part of RNA and DNA viruses.[20, 21]

Currently, several clinical trials are ongoing to investigate the role of these agents at antithrombotic therapeutic dosage against SARS-CoV-2 infection,[18] in order to reduce arterial thrombotic events or venous in moderate-to-severe COVID-19 cases, as well as reducing hospitalization and mortality.[22]

To date the recommendations of the main international scientific societies (American College of Chest Physicians; American Society of Hematology; International Society of Thrombosis and Hemostasis; National Institute of Health)[5] are:

- in patients treated at home, prophylactic antithrombotic therapy not indicated;
- in hospitalized patients with high thromboembolic risk, therapy at high dose with fractional-heparin to be preferred to NOACs;
- after hospital discharge, it may be reasonable to maintain prophylactic therapy with LMWH or a non-vitamin K antagonist oral anticoagulant (NOAC) at home for 7-14 days up to 6 weeks in case of pre-existing or persisting VTE risk factors (*i.e*., advanced age, long stay in ICU, severe immobility, Body Mass Index [BMI] >30 kg/m^2, previous VTE, active cancer, thrombophilia);
- in patients with evidence of PE or DVP, therapy with fractionated-heparin during hospitalization preferable to NOAC, continuing the therapy for at least 3 months; thrombolysis only in cases of cardiogenic shock or severe hypotension.

At this regard, The Food and Drug Administration approved trials for the use of rivaroxaban (PREVENT-HD Trial) or apixaban (ACTIV-4 Trial) post-discharge as VTE prophylaxis in patients with high-risk score of IMPROVE or altered coagulation parameters.[23-25]

Conclusions

In conclusion, SARS-CoV-2 infection has worldwide significant impact; from the first studies the pivotal role of thrombotic complications was highlighted, both in the arterial and venous districts, in determining acute complications, especially mortality, in patients with acute infection; as regard, the use of anticoagulants at preventive doses, and in some selected patients at therapeutic doses, have shown efficacy in reducing mortality, complications and length of hospitalization; elements of recent interest are the prothrombotic aspects in some patients during the follow-up after acute infection, and to date only high-risk patients would benefit from anticoagulant treatment after discharge from the hospital. Both LMWH and NOAC can have beneficial effects and helpful use in the treatment of the patients due to their antithrombotic effect as well as their anti-inflammatory properties; further studies are requested to explain and define these aspects.

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