Pulmonary embolism and COVID-19: A paradigm change☆

Tromboembolismo pulmonar y COVID-19: un cambio de paradigma

Dear Director,

On December 31, 2019, an outbreak of pneumonia caused by a novel coronavirus named SARS-CoV-2 was detected in the city of Wuhan (China). From a clinical point of view, infected patients could present with anything from mild upper respiratory tract symptoms to severe pneumonia associated with respiratory distress syndrome that could progress to severe respiratory failure and death of the patient.

Although this new disease mainly affects the respiratory tract, several observational studies suggest that SARS-CoV-2 (COVID-19) infection predisposes patients to thrombotic events in the vein; pulmonary embolism (PE) is the most frequent among them.[1–7] This increase in pulmonary thrombotic manifestations has been observed in the autopsies of patients infected in the SARS-CoV and MERS-CoV epidemics of 2003 and 2012, respectively.[8]

The physiopathology that links PE and SARS-CoV-2 infection is not well known, though it seems to be related to a state of hypercoagulability. Recent studies have demonstrated that D-dimer levels greater than 1,000 ng/mL in patients with COVID-19 constitute a prognostic factor that is relevant to mortality.[9] The systemic inflammatory response and endothelial damage associated with viral infection could activate coagulation, with an increase in thrombin generation and a decrease in the organism's natural anticoagulants. Years ago, the term ''immunothrombosis'' was coined to describe this correlation between the immune system and the coagulation system as a response to infection designed to prevent its propagation.

SARS-CoV-2 penetrates alveolar epithelial cells through the angiotensin-converting enzyme 2 (ACE2) surface receptor.[10] Viral replication triggers the activation of the complement system, with formation of C3a and C5a, which are able to recruit neutrophils, macrophages, lymphocytes, and monocytes that in turn are responsible for the massive release of proinflammatory cytokines (IL-1, IL-6, IL-8, and interferon-γ). These favor the expression of the tissue factor (TF) of thrombomodulin and endothelial adhesion molecules and also activate fibrinolysis, among other effects.[11]

Furthermore, SARS-CoV-2 infects endothelial cells that express ACE2. This endothelial damage activates the TF, which generates thrombin from prothrombin by means of activated factor X action. The activated circulating platelets coagulate and provide an appropriate phospholipid surface for the adhesion of different compounds in the coagulation cascade, with the generation of a large amount of thrombin.

Recently, Ciceri et al. have proposed the acronym Micro-CLOTS (*microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome*) to designate this pulmonary thrombotic microangiopathy or thrombosis *in situ*.[12] In concordance with this pathophysiological hypothesis, fibrin clots have been found in small pulmonary artery vessels in the autopsies of patients who have died due to COVID-19.[13]

For this reason, it would be interesting to learn the incidence of deep vein thrombosis (DVT) in patients with COVID-19 and PE. According to published series, the presence of concomitant DVT varies between 35%–45% in patients with PE.[14] Though 20% of patients with PE can present with undiagnosed DVT, the studies by Poissy et al.[4] and Lodigiani et al.[6] observed an incidence of DVT of 13.6% and 10%, respectively, in patients with COVID-19 and PE. The published case series of patients with COVID-19 and DVT are shown in Table 1.

In conclusion, the severe respiratory failure that patients with COVID-19 develop may partially be explained by pulmonary thrombotic microangiopathy that is the consequence of an exaggerated immune response in the host. The coagulopathy in these patients has led to the proposal of different antithrombotic strategies, especially in severe patients admitted to intensive care units (ICU). Although we do not know the best antithrombotic strategy, low-molecular-weight heparins at prophylactic or intermediate doses should be indicated in these patients (except when contraindicated). Therapeutic anticoagulation should be reserved for cases in which thrombosis is observed or suspected.[15]

Randomized controlled trials are needed to determine the suitability of primary thromboprophylaxis beyond discharge from the hospital and the optimal duration of anticoagulant treatment in patients with PE.

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Table 1 Case series of patients with COVID-19 and VTE.

Study	Number of patients	Study scope	Incidence of VTE (n; %)	Antithrombotic therapy regimen	Type of event
Klok et al.[1]	184	ICU	26 (14.13)	Prophylactic heparin	25 patients with PE One patient with DVT Other: one DVT in the upper limb associated with a catheter and 3 strokes
Llitjos et al.[2]	26	ICU	18 (69) with venous thrombosis in the LL and 6 (23) with PE	8 patients with prophylactic heparin	6 patients with PE
				18 patients with therapeutic heparin	14 patients with DVT 4 patients with SVT
Cui et al.[3]	81	ICU	20 (25)	Not administered	20 patients with DVT
Poissy et al.[4]	107	ICU	22 (20.6) with PE and 5 (4.7) with DVT	20 patients with prophylactic heparin	22 patients with PE; 3 patients with concomitant DVT (13.6%)
				One patient with VKA One patient with therapeutic heparin	5 patients with DVT
Lodigiani et al.[5]	388	ICU and HU	16 (4.4)	100% of ICU patients with prophylactic heparin 75% of HU patients with prophylactic heparin	10 patients with PE; 1 patient with concomitant DVT (10%) 4 patients with proximal DVT One patient with distal DVT Other: 1 DVT in the upper limb associated with a catheter, 9 strokes, and 4 ACS
Helms et al.[6]	150	ICU	25 (16.7) with PE and 3 (2) with DVT	Prophylactic heparin	25 patients with PE 3 patients with DVT Other: 2 strokes: one mesenteric ischemia and one peripheral artery ischemia
Middeldorp et al.[7]	198	ICU and HU	39 (20)	Prophylactic heparin	13 patients with PE 14 patients with proximal DVT 11 patients with distal DVT One patient with DVT in the upper limb

VKA: vitamin K antagonist; LL: lower limbs; ACS: acute coronary syndrome; PE: pulmonary embolism; VTE: venous thromboembolism; DVT: deep vein thrombosis; SVT: superficial vein thrombosis; ICU: intensive care unit; HU: hospitalization unit.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Whether to make decisions ön the flyŕegarding treatment for SARS-CoV-2 infection☆

Tomar o no tomar «decisiones en caliente» respecto al tratamiento de la infección por SARS-CoV-2

Dear Director,

The outbreak of the COVID-19 pandemic is a challenge of enormous dimensions for healthcare professionals, public health, and politicians.

As of April 5, 2020, official figures revealed that there were 135,032 people infected, 13,055 deaths, and 59,662 patients hospitalized (https://covid19.isciii.es/). We lived through convulsive days in which treatment protocols for COVID-19 infection were modified practically daily based on new evidence and the need to optimize the scarce therapeutic arsenal available.

Just three weeks ago, we learned the results of a clinical trial that compared lopinavir/ritonavir to supportive treatment in severe patients hospitalized with COVID-19 infection whose primary outcome was time until clinical improvement.[1] The poor overall results in terms of clinical response and mortality led, in just a few hours, to a rare wave of pessimism among the groups of professionals in charge of making decisions in many hospitals. This was reflected in heated discussions via WhatsApp and other forums, leading to the abrupt removal of lopinavir/ritonavir from the treatment protocols of several large centers in our country.

Nevertheless, the result of the information from a trial such as that one must be taken cautiously and analyzed with a critical, rigorous eye. The work suffers from various methodological problems in the design and in patient recruitment related to the urgent nature of the work. The authors themselves recognize these aspects in the discussion. Patient assignment was not blind and the desirable placebo control was not able to be established for patients who did not receive the drug in said study. Likewise, plasma levels of lopinavir/ritonavir were not able to be determined and could have been compromised in critical patients.

On the other hand, the study lacks power for outcomes that are secondary in the design, but which are important, such as mortality. Assuming the same premises as for the principal variable, between 200 and 860 additional patients would have been needed in each arm to demonstrate differences. In addition, although the overall benefit was weak, a close reading allows for observing how the use of lopinavir/ritonavir could point towards a trend in mortality reduction if it is used in the first 12 days. Among patients

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