Review Article

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Prevention of venous thromboembolism in COVID-19 patients: Is there a way forward?

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Introduction

Severe acute respiratory syndrome coronavirus 2 genome encodes approximately 25 proteins needed by the virus to infect humans and to replicate. The virus enters the human cell through the angiotensin-converting enzyme 2 receptors, which is expressed on the many tissues: vascular and respiratory endothelium, alveolar monocytes, macrophages, heart, kidney, and gastrointestinal tract.[1]

In the early months of 2020, the scientific community generally assumed that COVID-19 was an infective-inflammatory disease-producing pneumonia, acute respiratory distress syndrome, sepsis, and eventually multiorgan failure. Nevertheless, it was soon realized that it produced also cardiovascular thrombotic events such as deep-vein thrombosis (DVT) and pulmonary embolism (PE), arterial thrombosis (limb and gangrene), myocardial infarction, and eventually, liver and renal failure.[2,3]

Endothelial Cell Direct Viral Injury

Wichmann *et al*. reported the autopsy findings of the first 12 patients with COVID-19 that died in Hamburg (Germany). In Germany, it was a legal requirement to perform an autopsy for patients dying with a polymerase chain reaction-confirmed diagnosis of COVID-19. Autopsy revealed DVT in 7 of 12 patients in whom venous thromboembolism (VTE) was not suspected before death and PE was the direct cause of death in 4 of the 12 patients. In addition, the authors reported lymphocytic infiltration of the myocardium that might be responsible for the electrocardiographic changes observed in the absence of myocardial infarction.[4] Subsequently, the medical community became aware of the direct viral injury to the vascular endothelium which also contributes to the vascular complications.

Hemoglobin Dysfunction and Anemia

Hemoglobin values are reduced in COVID-19 patients with severe disease.[5] In addition, there is functional inhibition of hemoglobin by binding of the virus to the beta chains of Hb resulting in reduced oxygen transport and hypoxia. As a result, there is vasodilatation with pulmonary vasoconstriction with fibrin formation in lung microcirculation.[6]

Ackermann *et al*. investigated morphologic changes in the peripheral lung of patients who die from COVID-19 examining lungs obtained during the autopsy. Histologic studies showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were nine times as prevalent in patients with COVID-19 compared with patients dying from influenza.[7]

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An additional interesting information is that laboratory findings and clinical features of COVID-19 patients resemble high altitude pulmonary edema.[8] In COVID-19 patients, a typical feature is a "silent hypoxia" with normal PCO_2. PCO_2 increases above normal levels only at late stages of the disease. In addition, the virus increases circulating and tissue ferritin, which induces iron deficiency with further lack of functional hemoglobin.[9]

In summary, the main cellular and pathological effects of the virus are activation of coagulation, damage to vascular endothelium, decrease in endothelial NO, decrease in functional hemoglobin, hypoxemia and systemic hypoxia, ferroptosis with oxidative stress, and degeneration of mitochondria.[10]

Activation of Coagulation Factors

COVID-19 inflammation stimulates massive production of cytokines, which in turn increase the production of clotting factors by the liver. For example, fibrinogen, which is normally between 2 and 4 g/L and increases to 5–6 g/L in pregnancy (which is considered a hypercoagulable state), augments to 10–14 g/L in patients with COVID-19 infection.[11] Increased levels are also reported for lactate dehydrogenase, C-reactive protein, D-dimer, coagulation factors VIII and XII, ferritin, interleukin-6, and troponin, which indicates myocardial damage. In severe disease, there is an increase in prothrombin time and international normalized ratio; there is also a decrease in activated partial thromboplastin time and in antithrombin levels.[12]

Incidence of Venous Thromboembolism

Early studies from China highlighted a 20%–40% incidence of VTE in intensive care unit (ICU) patients in the absence of pharmacological prophylaxis[13,14] and a study including 184 patients in ICU from three academic medical centers in the Netherlands, reported that 31% patients developed VTE despite pharmacological prophylaxis.[15] In another early study by Middeldorp *et al*., symptomatic VTE was found in 13% of a series of 198 patients and after screening 55 of these patients with ultrasound a further group of 14 (7.1%) were found to have DVT. The clinical outcomes were much higher in ICU than in the ward and VTE was associated with death (HR 2.7, 95% confidence interval [CI] 1.3–5.8). The raised HR was still significant after adjustment for age, sex, and ICU stay (HR 2.4 95% CI 1.02–5.5).[16]

In 137 patients with COVID-19 pneumonia contrast computed tomography (CT) pulmonary angiography was performed. This was done in 63 outpatients to differentiate between pneumonia and PE. It was also performed in 72 in hospital patients because of clinical deterioration and increased oxygen needs. PE was found in 32 (24%) patients. In these 32 patients, PE was proximal in 10, segmental in 18, and multiple subsegmental in 4.[17]

Many other studies followed confirming the high incidence of VTE in patients with COVID-19 and in a recent meta-analysis of 40 studies involving 7966 COVID-19 patients the incidence of DVT and PE in the ICU was 25% and 17%, respectively; it was 7% and 4% in non-ICU patients. In studies in which screening with ultrasound and CT-angiography was performed the incidence of DVT and PE in ICU was 33% and 22%, respectively.[18]

An expert guidance statement issued in 2020 recommended escalated thrombophylaxis-doses such as therapeutic-doses of anticoagulation or intermediate-dose anticoagulation pending the results of randomized controlled trials (RCT).[19] However, subsequent RCTs failed to demonstrate benefit. A RCT evaluating safety and efficacy of therapeutic dose versus standard-dose thrombophylaxis was halted for futility in December 2020 after 1123 patients had been enrolled. There was no benefit and a high probability of harm with the therapeutic dose. However, in COVID-19 patients not in ICU, therapeutic dose was more effective than standard dose with regard to organ-support free days.[20] The INSPIRATION RCT which was published in March 2021 and involved 562 COVID-19 patients from 10 academic centers did not demonstrate any difference between intermediate dose and standard dose for the primary efficacy outcome (arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days) which was 45.7% versus 44.1%.[21] An observational study involving 2809 COVID-19 patients admitted to ICU found no benefit of therapeutic dose versus standard dose thrombophylaxis.[22] As a result, there was a growing body of evidence against dose-escalated thronbophylaxis and the American Society of Hematology 2021 Guidelines recommended prophylactic doses of low-molecular-weight heparins (LMWH) pending the results of RCT.[23]

In a recent RCT, 243 outpatients with COVID-19 were randomized to sulodexide or placebo. Sulodexide was associated with reduced hospitalization (RR 0.6; 95% CI 0.37–0.96. P =0.03) and reduced need for oxygen support (RR 0.71; 95% CI 0.5–1.0; P = 0.05).[24] Sulodexide is a natural glycosaminoglycan, which has a protective effect on vascular endothelium and has been shown to produce a 50% reduction in VTE recurrence when used

for 2 years in a RCT of extended prophylaxis without any increase in bleeding.[25]

Conclusions and Rationale for the Development of Effective Venous Thromboembolism Prophylaxis

The conclusions are that in patients with COVID-19 there is (i) activation of coagulation, as an acquired thrombophilia due to the virus, (ii) direct damage to the vascular endothelium, (iii) decreased function of hemoglobin producing hypoxemia, (iv) alveolar edema and microcirculatory thrombosis, and (v) DVT and PE resistant to prophylactic LMWH. Therefore, in patients with already compromised ventilation and impaired oxygen transport, it is not surprising that even a small PE may be fatal.

In addition to the activation of coagulation and damage to vascular endothelium by the virus, positive pressure ventilation in the ICU induces also a reduced lower limb blood flow and venous stasis. In other words, there is full activation of Virchow's triad. It is not surprising that COVID-19 patients in ICU are at very high risk for VTE and past experience teaches us that in such very high risk patients a combination of different prophylactic modalities is needed to reduce VTE incidence.

Thus, the high incidence of VTE resistant to prophylactic or therapeutic LMWH therapy in patients with COVID-19 is probably the result of the pleiotropic effect of the virus and it requires therapy with pleiotropic actions. It requires the use of combined methods of prophylaxis such as LMWH with intermittent pneumatic compression, a combination that has already been shown to be effective in high risk non-COVID-19 patients.[26] The most recent demonstration of the superior efficacy of combined modalities in the prevention of VTE in high risk patients is by the IPS: SUPER RCT.[27] In this study, 407 patients who underwent major surgery and had a Caprini score of ≥11 were randomised to receive either IPC in addition to standard prophylaxis with anti-embolic stockings (pressure of 18–21 mm Hg at the ankle) and LMWH (IPC group) or standard prophylaxis alone (control group). The primary outcome was asymptomatic venous thrombosis of the lower limbs, as detected by duplex ultrasound scan performed before inclusion to the study and every 3–5 days after surgery. The primary outcome occurred in 1 (0.5%) patient in the IPC group and 34 (16.7%) patients in the control group (relative risk, 0.03; 95% CI: 0.01–0.21). PE occurred in none of the 204 patients in the IPC group and in 5 (2.5%) patients in the control group (relative risk, 0.09; 95% CI, 0.01–1.63), and postoperative death occurred in six (2.9%) patients in the IPC group and 10 (4.9%) in the control group (relative risk, 0.50; 95% CI, 0.50–1.60).

Conclusion

In patients with COVID-19 in the ICU, there is a need for a clinical trial to determine the efficacy of not only the well-established combination of LMWH and intermittent pneumatic compression plus antiembolism stockings but also adding a drug such as sulodexide that protects the endothelium. In this situation, LMWH should alleviate the hypercoagulable state, sulodexide should protect the endothelium and intermittent pneumatic compression in combination with antiembolism stockings should increase venous return and blood velocity in the lower limb veins. The need for such a study is urgent.

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Conflicts of interest
There are no conflicts of interest.

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