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Response to 'What does monitoring platelet counts in COVID-19 teach us?'

Dr Jecko Trachil stressed the possibility of platelet consumption forming pulmonary thrombi in patients with COVID-19,[1] which coincides with the theory we are working on right now that pulmonary thrombi may be responsible for hypoxemia before typical acute respiratory distress syndrome develops,[2] called silent hypoxemia by some experts.[3] As for anti-platelet drugs attenuating thrombi formation, the balance would be too delicate to maintain, because they may interfere with the platelet blocking viral invasion.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Anticoagulant and antiarrhythmic effects of heparin in the treatment of COVID-19 patients

Most severe manifestations of COVID-19 cases, such as multiple organ failure and death, have been linked to coagulation dysfunction markers, such as platelet reduction and increases in prothrombin time, fibrin degradation products, and, mainly, D-dimer.[1] A recent paper by Tang et al[2] in this journal reported that heparin treatment reduced mortality of COVID-19 patients with elevated D-dimer; similar preliminary results have been reported elsewhere.[3] A mounting body of evidence shows that SARS-CoV-2 causes a "cytokine storm"[1,4] that activates the coagulation cascade, leading to thrombosis. Similar to the findings in severe sepsis, generalized deposition of intravascular thrombi compromises the blood supply of several organs, leading to organ failure.[5]

Disseminated intravascular coagulation secondary to severe infection is classically associated with gram-positive and gram-negative bacteria, malaria, and other hemorrhagic fevers, such as hemorrhagic dengue, although SARS-CoV and MERS-CoV have also been shown to trigger disseminated intravascular coagulation. Similar results in COVID-19[2-4] now suggest that widespread coagulation events significantly contribute to worse outcomes and patient mortality, which might be attenuated by anticoagulant treatment.

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We would also like to add that, although a direct anticoagulant effect is likely crucial to the therapeutic effect of heparin, it also has antiarrhythmic properties[6,7] that could show promise in the treatment of COVID-19, in which cardiac arrhythmias are the immediate cause of several patient deaths.[4] Heparin oligosaccharides have a marked antiarrhythmic effect in an animal model of heart ischemia-reperfusion, as well as in isolated rat atria, reducing both ventricular arrhythmias and atrioventricular block, likely by increasing Na^+-Ca^{2+} exchanger activity.[6]

About 16% of COVID-19 patients show cardiac arrhythmias and 7.2% had acute cardiac lesions.[4] Increased cardiac lesion markers, such as interleukin-6, high-sensitivity troponin I, and lactate dehydrogenase are correlated with poorer patient outcomes.[4] COVID-19 increases troponin I and these higher levels correlate with more frequent complications, including malignant ventricular arrhythmias.[4] There are many reports of fulminant myocarditis with cardiogenic shock, associated with atrial and ventricular arrhythmias.[1,4] In a recent report on Wuhan COVID-19 patients, 16.7% of all hospitalized patients and 44.4% of intensive care unit patients had cardiac arrhythmias.[8] Besides, several drugs proposed for use in the treatment of COVID-19, such as hydroxychloroquine (HCQ), block voltage-gated K^+ channels, which may cause drug-induced long QT syndrome and atrioventricular blocks.[9] Therefore, the concomitant use of HCQ and other antiarrhythmic medications, such as amiodarone or sotalol, may further increase the QT interval and require close electrocardiogram monitoring. Further characterization of arrhythmic load and mechanisms of death are critical to guide additional treatments and preventive strategies, including the potential role of cardioversion. Azithromycin and other macrolides have also been combined with chloroquine and derivatives in COVID-19 patients, but these antimicrobial drugs also induce long QT.[9] Combined HCQ-azithromycin-treated patients are at an increased risk for drug-induced long QT syndrome and *torsades des pointes*. Lopinavir and ritonavir also prolong PR and QT intervals and may cause severe atrioventricular blocks and *torsades de pointes*.[10]

Hypokalemia may also increase vulnerability to several tachyarrhythmias and, therefore, COVID-19 patients will likely require close electrolyte and QT monitoring whenever treated with HCQ-azithromycin because of the interactions of SARS-CoV2 with the renin-angiotensin-aldosterone system and the likelihood of hypokalemia.[1,2] The American College of Cardiology now offers an easy-to-use calculator to help medical professionals in determining which patients are at an increased risk for ventricular arrhythmias when treated with HCQ-azithromycin. Other HCQ interactions in COVID-19 risk groups may include antihypertensive drugs, such as beta antagonists and Ca^{2+} channel blockers, leading to severe bradycardia and cerebral hypoperfusion.[9]

Neither Tang et al[2] nor Negri et al[3] report any increase in bleeding with heparin treatment, though this might be a concern with other COVID-19 drug combinations. For instance, lopinavir/ritonavir inhibit CYP3A4 and may drastically increase Xa factor inhibition when combined with apixaban or rivaroxaban.[10]

The use of heparins in the treatment of patients with COVID-19 is likely to be beneficial and effective because it combats the coagulopathies that lead to hypoxia and generalized organ failure, but also because it is likely to attenuate cardiac arrhythmias and sudden deaths associated both with COVID-19 itself or with its pharmacological therapy. It remains to be seen whether other antiarrhythmic drugs also have a role to play in the treatment of COVID-19, at least in patients at higher risk for cardiac arrhythmias.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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All those D-dimers in COVID-19

One of the most consistent abnormal hemostatic laboratory markers in COVID-19 is raised D-dimers. Increased D-dimers have also been observed in several studies published in the *Journal of Thrombosis and Haemostasis* to have prognostic implications.[1,2] But, some of the perplexing questions in this regard are what may be the reasons for such marked elevation in D-dimers and may it have any "useful" purpose apart from prognostication?

SARS-CoV-2 is primarily a respiratory pathogen. An overlooked host defence mechanism to counter this virus is the activation of lung-specific coagulation system, otherwise termed broncho-alveolar hemostasis.[3] In healthy individuals, the coagulation-fibrinolysis balance of the broncho-alveolar hemostasis is shifted toward fibrinolysis.[4] This high fibrinolytic activity (predominantly urokinase plasminogen activator) diligently clears fibrin deposited in alveolar compartments and allows uninterrupted gas exchange.[4] However, in patients who develop acute lung injury secondary to COVID-19 (and other infectious states), this balance shifts toward the procoagulant side, with the purpose of creating pulmonary thrombi possibly to limit viral invasion.[3-5] Of course, the breakdown of these thrombi would cause an increase in D-dimers. But may there be other causes of these elevated D-dimers?

Coagulation and fibrinolysis do not always occur in the intravascular space, especially in the lungs. Wagers and colleagues have shown that one of the prominent features of airway inflammation is the leakage of plasma proteins including fibrinogen and thrombin into the airway lumen.[6] This elegant study demonstrated extravascular thrombin to convert fibrinogen into fibrin, which contributed to airway hyper-responsiveness.[6] The physiological purpose of this extravascular fibrin is possibly to serve as a matrix on which inflammatory cells can attach and function.[7] This extravascular fibrin breakdown could also explain the marked increase in D-dimers noted in patients with malignancies even in the absence of clots in the circulation.[8]

How is the extravascular fibrinolysis relevant to COVID-19? The intense lung inflammation caused by SARS-CoV-2 is associated with elevated fibrinogen levels. Cross-linked fibrin generated from the markedly increased fibrinogen that leaks into the extravascular space would be broken down by plasmin or proteolytic enzymes released from activated neutrophils.[9] D-dimers formed in this manner may not signify thrombus formation but could predict the need for mechanical ventilation, because they arise from lung exudates.

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