Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Cardiac injury and COVID-19 associated coagulopathy assessed by rotational thromboelastometry tests: Keep on searching for the right path

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Evidence based medicine has shown an increased morbidity and mortality in patients with coronavirus disease 2019 (COVID-19) associated cardiac injury and coagulopathy [1–4]. There is massive thrombin formation with micro- and macro-angiopathic thromboembolic complications in symptomatic patients with COVID-19 associated coagulopathy (CAC) [5,6]. The typical laboratory findings are elevated plasma levels of D-dimer and fibrinogen, as well as, increased clot strength measured by rotational thromboelastometry tests in these CAC patients [7]. This COVID-19 pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the data from the World Health Organization (WHO; https://covid19.who.int/), globally, as of 4th February 2022, there have been 386,548,962 confirmed cases of COVID-19, including 5,705,754 deaths, reported to WHO. As of 2nd February 2022, a total of 10,040,768,270 vaccine doses have been administered.

The COVID-19 infection begins when the S-protein of SARS-CoV-2 binds with the patient receptor angiotensin-converting enzyme 2 (ACE2) from the upper respiratory mucous membrane cells [8]. ACE-2 transforms angiotensin (ANG) I and II to cardioprotective peptides, ANG 1–9 and ANG 1–7, hence, its downregulation may increase heart and vascular damage. The ACE-2 deprivation may aggravate endothelial dysfunction, and clot formation [9]. The fact that ACE-2 is already reduced in vessels with established atherosclerotic plaques and in diabetes mellitus, may explain, in part, the deleterious outcome in the patients with COVID-19 [10]. The resultant decreased ACE-2 generates cytokine release with exacerbation of cardiac symptoms and underlying cardiovascular diseases [11]. Therefore, it seems rational to assume that endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. Endothelial dysfunction activation results in the loss of anticoagulant molecules which leads to further synthesis of procoagulant molecules, namely, thrombin, von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), tissue factor (TF) and platelet activating factor [1]. The anticoagulant and antithrombotic molecules consist of thrombomodulin, tissue plasminogen activator, heparin sulfate, and antithrombin. The pro- and anti-coagulant molecules are present in activated endothelial cells, platelets, and megakaryocytes. Therefore, the endothelial dysfunction with deprivation of anticoagulant molecules on one hand, and increased procoagulant molecules on the other hand, favors thrombosis and CAC [1].

In the present issue of *Advances in Medical Sciences*, Capone et al. [12] present a study on traditional coagulation and whole blood rotational thromboelastometry tests in COVID-19 patients with and without cardiac injury. The authors should be commended for their efforts analyzing possible mechanisms of coagulopathy in patients with COVID-19-associated cardiac injury. They studied in their retrospective, single center, cross-sectional research, 104 consecutive hospitalized patients with laboratory-confirmed COVID-19. A total of 40 (38%) patients developed cardiac injury defined as having increased levels of high-sensitivity cardiac troponin I (hs-cTnI). The authors found no significant differences in coagulation parameters between patients with and without cardiac injury. In addition, they found abnormal maximum clot firmness (MCF) levels in 80 (77%) patients. When patients with and without cardiac injury were compared, no significant differences in MCF values, and percentage of abnormal MCF were detected. They observed that cardiac injury, but not hypercoagulability, was significantly associated with mortality. Therefore, the authors concluded that there are no differences in traditional coagulation and rotational

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thromboelastometry parameters among hospitalized COVID-19 patients with and without cardiac injury.

A hypercoagulable state is seen due to several coagulation abnormalities [13]. Although, hypercoagulation is a relatively frequent alteration in COVID-19, there were no significant differences in coagulation parameters between COVID-19 patients with and without cardiac injury in the study by Capone et al. [12]. The complex process of coagulation is influenced by multiple factors - which are interrelated pathophysiological elements, namely, diffuse cytokine release, elevated ANG II, endothelin-1, vWF, PAI-1, TF, reactive oxygen species (ROS), and extrinsic clotting cascade [14]. The diffuse cytokine storm, ROS and proteases from activated neutrophils in COVID-19 patients may damage the endothelial cells gap junctional proteins of the vasculature, resulting in further *trans*-endothelial migration of neutrophils. Degranulated neutrophils release damage-associated molecular proteins, which continue altering the junctional proteins and endothelial layer. This ongoing vascular damage leads to greater serum contact with subendothelial tissue and thrombus formation through activation of vWF, the coagulation cascade, and platelet adhesion [15]. Moreover, the systemic inflammation leads to increased levels of PAI-1, which enhances endothelial fibrin deposition and reduced thrombolysis leading to the hypercoagulable state and clot formation observed in patients with COVID-19. As observed by Capone et al. [12], the coagulation profile denotes thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and short activated partial thromboplastin time in COVID-19 patients. Tang et al. [16] demonstrated in their study that elevated levels of D-dimer was observed in more than two thirds of patients with COVID-19, and was associated with illness severity and mortality. These alterations in the coagulation status predispose patients to hypercoagulability states, thromboembolic complications, and increased risk of disseminated intravascular coagulation, and multi-organ failure.

The authors of the Capone et al. study [12] did not explore all aspects of the complex and diverse coagulation processes. Platelets play an important role in this context in patients with COVID-19. Hypercoagulability may lead to coronary microvascular thrombosis with increased plasma troponin levels pointing out to microthrombi as the most likely motive of myocyte necrosis in patients with COVID-19 [17–19]. Fox et al. [20] have shown platelet–fibrin thrombi and intravascular megakaryocytes in the small vessels of all major organs. They observed, in the microscopic findings, inflammatory damage, congestion with luminal platelet rich fibrin deposition and angiogenesis in the capillary vessels [20]. However, the authors of the Capone et al. study [12] did not perform viscoelastic tests to evaluate platelet function and thrombin mediated platelet activation to shed more light on the complex interactions between endothelium and platelets that finally terminates with the development of the platelet rich thrombi. Although whole blood rotational thromboelastometry tests performed in the Capone et al. study [12] is a reliable tool to analyze coagulation disorders, some unknown pro-coagulable mechanisms involved in the COVID-19 pathophysiology may have gone undetected. As the authors pointed out, other useful tests such as thrombin generation or platelet reactivity tests were not performed.

On the contrary, the mechanisms for the cardiac injury observed in 38% of the patients studied by Capone et al. [12] may have several explanations other than hypercoagulability. Indeed, several mechanisms may be implicated in the development of cardiac injury in patients with COVID-19. The presence of several cardiovascular risk factors and the elevation of plasma myocardial biomarkers make the possibility of myocardial ischemia paramount. Another possible cause is type 2 myocardial infarction secondary to severe hypoxia and hypotension increasing the cardiometabolic demand and intracellular calcium levels which may develop myocardial damage in severely ill COVID-19 patients. Moreover, the elevation of plasma myocardial biomarkers may result from acute myocarditis induced by SARS-CoV-2 direct impact on the myocardial cells leading to inflammation and apoptosis-induced cellular damage [17–19]. Varga et al. [21] have shown viral elements found inside the endothelial cells suggesting direct invasion by SARS-CoV-2. This fact is facilitated by the high number of ACE-2 receptors found in the endothelial cells favoring cell invasion. In addition, increased level of catecholamines, due to COVID-19-associated emotional or physical stress, further worsens myocardial damage and microvascular dysfunction [17]. There is more than 6-fold higher mortality in hospitalized patients with COVID-19 who have elevated cardiac Troponin T levels which persisted after adjustment for baseline characteristics and medical comorbidities [22]. Therefore, it is a plausible initiative to perform measurements of plasma myocardial biomarkers immediately after hospitalization for SARS-CoV-2 infection in order to identify a subset of COVID-19 patients with possible cardiac injury and CAC that may progress towards a worse clinical outcome.

As the authors of the Capone et al. study [12] mentioned, some coagulation tests were not available in all patients in their retrospective study. In addition, studies with retrospective design and uncontrolled confounders might bias the real impact, and the influence of hypercoagulability parameters in COVID-19 patients with associated cardiac injury. Therefore, large-scale, prospective studies are needed to clearly define its influence. Further clinical investigations should be designed to prospectively study all components of the coagulation process, and to define in detail the role and true influence of hypercoagulability in COVID-19 patients with cardiac injury. This endeavor is a wanted necessity not only to keep on searching, but to find the right path.

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