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Letter to the Editors-in-Chief

Don't let D-dimer fool you: Elevated D-dimer plasma levels should not imply 'hyperfibrinolysis'

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Dear Editor,

We read with interest the letter by Nielsen N.D. and coll. [1] dealing with D-dimer and fibrinolysis in COVID-19 patients. The authors discussed the apparent discrepancy between increased D-dimer in and decreased fibrinolysis potential of the blood of COVID-19 patients. They proposed an extravascular origin for the observed increase in D-dimer plasma levels, which could solve the so-called paradox. This interesting discussion provides us with an opportunity to highlight some key points about D-dimer and the methods used to assess fibrinolysis.

In the first place, there is the difficult issue of what 'hyperfibrinolysis' actually is. Our view is that the term 'hyperfibrinolysis' should be restricted to clinical settings with massive release of plasminogen activators, and ensuing disseminated plasmin generation in so large amounts that circulating plasmin is not fully opposed by inhibitors (α2-antiplasmin…), which are overwhelmed; the result being lysis of endogenous fibrin hemostatic plugs, but also the breakdown of fibrinogen – which is called fibrinogenolysis – with elevated fibrinogen degradation products. This entity should be distinguished from increased fibrinolytic potential i.e. an increased ability to locally generate plasmin and/or hypersensitivity of fibrin clots to plasmin, but without significant levels of circulating plasmin. While hyperfibrinolysis is extremely worrisome and requires prompt medical attention, increased fibrinolytic potential would essentially be troublesome in presence of a hemostatic challenge.

Second, there is no need to postulate a 'hyperfibrinolytic state' to account for elevated D-dimer. Fibrin degradation products containing the 'D-dimer' motif, and hence the neoepitopes enabling specific detection with suitable monoclonal antibodies (in short 'D-dimer'), result from the plasmin action on cross-linked fibrin. D-dimer is therefore produced in any situation with fibrin deposits in the body, with its ensuing (at least in part) breakdown (e.g. cancer, inflammation, pregnancy, venous thromboembolism…); their production does require neither hyperfibrinolysis nor increased fibrinolytic potential. As a matter of fact, the amount of D-dimer produced could depend mainly on the total mass of deposited fibrin and the fibrin surface area available for plasmin action, though obviously, the extent of plasmin formation would play a role [2]. Furthermore, as the authors pointed out, D-dimer can originate from the breakdown of fibrin formed in the extravascular space, with no obvious link with plasma fibrinolytic activity. Extravascular fibrin deposits breakdown could involve distinct players (e.g., uPA, leukocytes proteases) acting locally [3]. Whether measurements in circulating plasma actors of fibrinolysis, of biomarkers such as plasmin-antiplasmin complexes or of plasma fibrinolytic potential have any relevance with what takes place extravascularly remains unclear. Elevated D-dimer levels therefore only indicate that cross-linked fibrin has been produced somewhere in the body, within or not the vasculature, without implying any kind of 'hyperfibrinolysis'.

The authors argued on by stating that the elevated D-dimer plasma levels in COVID-19 patients originate mainly from the breakdown of extravascular (pulmonary parenchyma) fibrin deposits. Such a hypothesis, which had already been raised [4], is supported by histopathological findings identifying significant fibrin deposition in alveolar and pulmonary microvascular compartments of severe COVID-19 patients [5]. In line with the assumption, we identified that plasma levels of fibrin monomers were low (i.e. within the reference range) in the plasma of most ICU COVID-19 patients in contrast to D-dimer, whereas both biomarkers increased in cases of intravascular thrombin generation (e.g. disseminated intravascular coagulopathy, arterial or venous thromboembolism) [6]. Fibrin monomers, which are associated with fibrinogen or related molecules (forming then so-called 'soluble complexes') have a much higher molecular mass than end-products of cross-linked fibrin degradation, containing the D-dimer motif, and hence would not be able to reach the vascular compartment if formed in the extravascular space [7]. This strongly suggests that the high baseline plasma levels of D-dimer observed in COVID-19 patients do indeed mostly originate from the extravascular space. Of note, using a so-called global fibrinolytic capacity test, we identified a decreased fibrinolysis potential in these patients [8], confirming other published observations using viscoelastometry testing [9].

Such an approach (thereafter referred to as VET) has been used for decades to detect major hyperfibrinolytic states in trauma patients and during perioperative hemorrhage, and was claimed to have potential usefulness in sepsis and trauma-induced coagulopathy to detect low levels of fibrinolysis and to identify patients to whom the administration of tranexamic acid should be avoided [10,11]. However, there are two crucial points to consider. First, endogenous systemic fibrinolysis is

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usually weak because of very low circulating levels of free plasminogen activators (such as t-PA) and clot lysis is a slow phenomenon, which is unlikely to occur significantly within the time frame of VET measurement (i.e., 30 to 60 min), unless an exogenous plasminogen activator is added. The second point stems from the previous one: several VET modifications have been reported to demonstrate hypofibrinolysis, but standardization has been lacking concerning the nature (t-PA versus u-PA) and the concentration of plasminogen activators, leading to wide variation in lysis parameters and variable results [12–16].

To conclude, the elevation of D-dimer levels in the plasma of COVID-19 patients mainly raises the question of their origin. Several lines of evidence point to a predominant extravascular origin of plasma D-dimer such as the observation of extensive fibrin deposits in the alveoli or the low baseline fibrin monomer plasma levels. Although basal D-dimer plasma levels are often elevated in COVID-19 patients, a further increase in case of a venous thrombotic event or disseminated intravascular coagulation is possible, but the determination of diagnostic thresholds becomes much more complicated. The resort to biomarkers specific to the intravascular compartment such as fibrin monomers could be more appropriate. Besides, we are in desperate need of a good test to assess the fibrinolytic system potential and activity in clinical practice; D-dimer is not suitable for such a purpose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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