Internal and Emergency Medicine (2020) 15:1369–1373
https://doi.org/10.1007/s11739-020-02443-8

IM-POINT OF VIEW

# COVID-19: The crucial role of blood coagulation and fibrinolysis

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Received: 22 June 2020 / Accepted: 9 July 2020 / Published online: 3 August 2020


**Abstract**
The overflow of studies in the recent literature on COVID-19 often gives provisional or contradictory results and therefore deserves pauses of reflection and reconsideration. In fact, knowledges of pathophysiology of this new disease are still in development and hence originate discussions and interpretations. Regarding the role of blood coagulation and fibrinolysis, these mechanisms should be considered as crucial especially in severe cases. It is proposed to consider two distinct phenotypes of thrombotic manifestations: the current "thromboembolic type" also occurring in other kinds of sepsis, and the diffuse micro-thrombotic type, prevailing in the lungs but sometimes extending to other organs. Both types can induce severe disease and are potentially lethal. The micro-thrombotic pattern, more specific for COVID-19, results from a massive activation of coagulation strictly coupled with a hyper-intense inflammatory and immune reaction. This results in widespread occlusive thrombotic micro-angiopathy with destruction of alveoli and obstructive neoangiogenesis. The involvement of fibrinolysis, often neglected, confers a double faceted process of activation/inhibition, finally conducive to a fibrinolytic shutdown that reinforces persistence of micro-thrombi. Considering these peculiar mechanisms, it seems evident that both prophylactic and therapeutic effects of current anti-thrombotic drugs cannot be taken for granted and need therefore new specific and rigorous controlled trials.

**Keywords** COVID-19 · Coagulation · Fibrinolysis · Micro-thrombosis · Immuno-thrombosis · CID

## Introduction

Across the rapidly overflowing literature on epidemiological, pathophysiological and clinical aspects of COVID-19 disease, the changes of blood coagulation and fibrinolysis mechanisms still include areas open for discussion and speculation, that may be useful for further research. Therefore, I appreciate this opportunity to present some "points of view" in a Journal of Internal Medicine.

## Pathology

The first suggestion about a crucial role of blood coagulation activation and thrombogenesis in the pathophysiology of COVID-19 disease came from anecdotal descriptions of autopsies of patients deceased for severe infection. Soon, formal observational studies showed that venous thromboembolism (VTE) occurred in about 30% of COVID patients admitted to intensive care units (ICU) in the Netherlands [1, 2]. Among VTE cases, pulmonary embolism (PE) occurred in 26% [1] and was significantly associated with death. The cumulative incidence of any type of venous or arterial thrombosis amounted to 49%, with a majority for pulmonary embolism with or without concomitant deep vein thrombosis (DVT) [1].

However, a particular type of thrombosis pattern captured attention: a severe and extensive organ-bound microthrombotic phenomenon, prevailing in lungs and associated with severe, often lethal respiratory failure [2]. A small number of cases of this pattern were also reported in other organs as kidney, brain, and even as "blue (or purple) toe".

Both mechanisms, the classic thromboembolic (Type 1) and the microthrombotic one (Type 2), showed to be potentially lethal, but the Type 2 pattern appeared more specifically bound to the worsening of severe respiratory failure [3]. The two patterns may occur as concomitant, separate, or sequential in the same patient.

The pathophysiology of Type1 mechanism can be envisaged as a particularly severe variant of the well known

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VTE developing in hospitalized non-surgical patients with acute or critical illness [4]. Indeed, the massive activation of blood coagulation observed in COVID-19 disease may explain the higher prevalence of VTE in comparison with non-COVID-19 patients. At any rate, it is unsettling to notice that in the reported series of patients this complication arose despite routine heparin prophylaxis, administered at times and doses for "hospitalized medical patients".

Conversely, the Type 2, microthrombotic pattern, appears as a more aggressive variant of similar manifestations observed in lethal cases of influenza or SARS. Major features consist in widespread microthrombosis in both lungs, extending to the whole respiratory area. The material found at autopsy inside microvessels and alveolar spaces was described as a mass of deteriorated thrombotic materials including damaged blood cells (erythrocytes, leukocytes, monocytes, platelets), and fibrin strands, with a fluid part ascribed to intra-alveolar hemorrhage. A detailed observation found in fact diffuse and severe endothelial and alveolar damage with disruption of alveolar membranes, peri-alveolar microangiopathy and widespread microthrombosis with intra-alveolar hemorrhages. A unique phenomenon associated with the above changes was uncontrolled neo-angiogenesis of the intra-alveolar type, i.e., by intussusception rather than exterior sprouting, resulting in a rapid occlusion of alveoli from the inside [5].

## Coagulation

What are the mechanisms of these double-faced thrombotic phenomena?

It is natural to surmise that the two distinct thrombotic patterns result from one and the same massive activation of blood coagulation, that assumes different pathologic features according to local factors, mainly related to different reactivity of the various tissues and their endothelium. These differences were very early observed by the group of Astrup [6], and have been more recently characterized in lung territories [7].

This type of activation of blood coagulation seems to be not only faster, but also more severe than that observed in other types of sepsis or life-threatening influenza. This peculiar coagulation activation was initially perceived as a close variant of disseminated intravascular coagulation DIC [8, 9] drome shares with DIC the marked elevation of D-dimer levels, the mechanisms of clotting activation seem different (see later), the degree of consumption of coagulation factors and platelets is much milder, there are no signs of hemolysis and no scistocytes, and a generalized fibrinolytic activation is missing, thus not supporting systemic but only local hemorrhages. Indeed, this pattern of thrombogenesis has been defined as "immuno thrombosis", or thrombo-inflammation [10], and is considered a distinct variant of DIC.

This particular clotting process is likely primed by a massive release, mainly from monocytes and endothelial cells, of cytokines, tumor necrosis factor and similar pro-inflammatory mediators (the cytokine "storm"), that activate coagulation Factor XII (the "contact" factor) thus linking coagulation with inflammatory and immunologic processes, and with the bradykinin system. It must be noticed at this regard that activation of factor XII is not necessarily involved in the usual patterns of hemostasis and thrombogenesis: in this particular activation model the complement becomes activated and participates in fibrin and cellular deposits at microvascular levels.

## Fibrinolysis

An important role must be attributed to the fibrinolytic system, connected not only to blood coagulation (as directly and indirectly stimulated by thrombin), but also to the renin-angiotensin system (RAA). In fact, a main component of RAA, the angiotensin-converting enzyme 2 (ACE 2), acts as a natural receptor for COVID19 and other similar viruses. After binding the virus, ACE2 is competitively consumed and Angiotensin II remains in excess, thus freely acting as a potent stimulator of the plasminogen activator inhibitor (PAI 1, the main inhibitor of fibrinolysis). At the same time, increased bradykinin resulting from the above quoted factor XII activation stimulates the main natural fibrinolytic agent, the tissue plasminogen activator (tPA) [11].

Fibrinolysis may thus undergo concurrent upgrading of activation (tPA) and/or inhibition (PAI I), inducing a prothrombotic or pro-hemorrhagic state according to sites and phases of the biologic process. Phase or sites of locally increased tPA activity may explain intra-alveolar bleeding, while phases or sites with increased PAI I inhibitory activity may favor persistence or worsening of microthrombosis and evolution towards pulmonary fibrosis. Moreover, a total fibrinolytic shutdown (hypofibrinolysis) has been recently demonstrated in blood of severe COVID-19 [12].

Summarizing, the unstable balance between activation and inhibition of fibrinolysis may explain the co-existence of thrombotic and hemorrhagic features in lungs, and also in other organs as kidney [13] and brain [14]. According to these tenable assumptions, that anyway deserve further confirmation, it can be recalled that the term "Pulmonary Thrombosis", an entity distinct from "Pulmonary Embolism or Thrombo-embolism", proposed by an Italian group [15] just before the COVID-19 era, can presently be attributed to the COVID-19 induced pulmonary microthrombosis [16].

## Other mechanisms

The present interpretation of the COVID-19 microthrombosis as due to a peculiar, immune-mediated hypercoagulation, and modulated by a complex fibrinolytic response, can still be discussed. An alternative view stresses some similarities with the microthrombotic derangement of thrombotic thrombocytopenic purpura (TTP) rather than of DIC [17]. TTP involves a severe diffuse microangiopathy due to heavy endothelial damage with release of large multimers of von Willebrand Factor (vWF) responsible for platelet aggregates and thrombosis. This process is normally inhibited by a metalloproteinase, ADAMST 13, that can be lacking due to several causes. The picture of TTP, differently from DIC, includes hemolytic anemia with scistocytes, severe thrombocytopenia, increase of circulating von Willebrand factor, normal PT, pTT and fibrinogen. However, this pattern is highly variable in the single cases, according to the plurality of the disease mechanisms. Among the data supporting the concept that COVID19 microthrombosis could be a variant of TTP, a contribution published in this Journal reports high levels of vWF and low levels of ADAMST 13 in severe patients, associated with poor prognosis [18]. This hypothesis could have therapeutic implications.

Hypoxia, obviously present in the COVID19 disease, is "per se" an important thrombogenic factor: examples of this pro-thrombotic effect are, for instance, sickle cell anemia, and high-altitude thrombosis. A reduced synthesis and release of the physiologic anticoagulant Protein S in hypoxic status, has been described as a possible cause of thrombosis [19].

Also features of redox abnormalities, as acquired hemoglobinopathy, iron overload in cells, increased ferritin, have been described and their therapeutic correction might be useful [20].

## Remarks on laboratory diagnosis

The parameter most often used to ascertain the coagulation-fibrinolysis activation is D-dimer, considered as predictive of a poor prognosis [21] and used as biomarker for calibration of anticoagulants, especially for heparin. However, it must be noted that D-dimer is sensitive to fibrin degradation products derived not only from coagulation, but also from fibrinolysis. D-dimer has limited specificity being positive also in inflammatory states without thrombosis. Thus, D-dimer should at least be coupled with one of the validated scores measuring the clinical risk of thrombosis, when used for choice and calibration of anticoagulants.

A further remark should be made about the prolongation of aPTT. This finding was initially considered as a sign of low-grade consumption of clotting factors, less pronounced than in classic DIC. However, in a number of studies aPTT prolongation was due to presence of the "Lupus like Anticoagulant (LAC)". Among 216 COVID19 patients positive for severe acute respiratory syndrome, 20% had a prolonged aPTT, and 91% of these were positive to LAC [20]. It can be noticed that many of these patients had also Factor XII reduction, bound to the above discussed peculiar activation pathway [22]. It is well known that the expression "Lupus *anticoagulant*" refers to a laboratory effect, while the corresponding clinical effect consists in a severe pro-thrombotic tendency. Therefore, this finding adds further evidence to the immunologic nature of the COVID19 coagulopathy, and may also have therapeutic relevance: far from discouraging antithrombotic treatments, it re-inforces their indication.

A further methodologic remark originates from the double function of fibrinolysis suggested above. Direct measurement of tPA and PAI I are certainly important, but in many instances and especially when both factors are elevated (as may happen in this condition), clinicians will ask for a definite answer: "in this patient, at this time, what is the state of fibrinolytic activity in blood?" For this reason, during the last years, we assisted to a retrieval of global tests, like Euglobulin lysis time, or thromboelastography (TEG), a method exploring the visco-elastic properties of fresh blood clots containing all physiological factors and actors of coagulation and fibrinolysis. This method was first proposed around the fifties of the twentieth century and was later almost abandoned. TEG was then re-born in Trauma Units, where a fast and definite answer is needed in front of patients with acute and severe bleeding. COVID19 patients rarely bleed, and in fact most of them have a fibrinolytic shutdown as demonstrated by TEG [12]. Although TEG was never very popular in coagulation laboratories, these and other recent data indicate that updated TEG techniques should be more widely adopted for clinical purposes.

## Remarks on therapeutic problems

First, it must be recalled that a number of papers, and especially a recent large observational study suggest that anticoagulant therapies are associated with lower mortality [24]. This study supports further observational studies or, whenever possible, controlled prospective trials. These have been difficult to plan because of the violence of the viral aggression, and will still be hampered by the welcomed reduction of more severe cases.

Regarding prophylaxis, it should be noticed, as said, that in a number of previous studies thrombosis occurred

*despite* prophylaxis with low-dose lmw heparin [1, 2]. This observation should be considered in planning new studies. An additional problem is posed by heparin resistance in COVID19 patients who had been treated with therapeutic doses of heparin [23]. Both these findings should be considered especially in patients at risk, or with evidence of recurrent thrombosis.

Synthetic Guidelines on anticoagulant and fibrinolytic treatments have recently been issued by a group of experts appointed by the American Society of Chest Physicians [25].

## Conclusions

This "point of view" is intended to describe the complex pathophysiology of the thrombotic and microthrombotic features of COVID19 disease. The more likely interpretation of these events still appears to be an immunologic variant of disseminated intravascular coagulation, associated with a complex fibrinolytic response with prevailing fibrinolytic shutdown in blood. However, other mechanisms, as severe hypoxia and possibly features of thrombotic thrombocytopenic purpura, may complicate the thrombogenic pattern, and require additional suggestions for therapy.

As a side-observation, at a first glance many (perhaps too many) of the findings described are "associated" with mortality or poor prognosis. It seems likely that this association could be a consequence of a selection bias, as most of the studies were made on severe patients, characterized by poor prognosis.

## Addendum

During the phase of submission of this paper, some of the mechanisms forwarded here as reasonable hypotheses have been substantiated and supported by solid experimental data. The pathogenesis of microthrombotic vasculitis has been clarified as due to a Type 3 hypersensitivity inducing microvascular deposition of immune complexes, with IgG, IgM, and complement fraction 3 on microvascular walls (Roncati et al. Clin Immunol, 2020, letter). Additionally, clinical and especially imaging observations have in turn found that the clinical "Pulmonary Embolism" in severe COVID-19 patients differs from classic pulmonary embolism (PE). In fact, in severe COVID-19 patients pulmonary thrombi are more frequently located in small- to mid-sized rather than in large pulmonary vessels, and a prevalence of PE versus DVT (Deep Vein Thrombosis) is also found, suggesting that COVID-19-associated pulmonary microthrombosis represents a combination of thromboembolic disease with immunothrombosis at the tissue level (Van Dam et al. Thromb Res, 2020).

**Acknowledgements** The Author is deeply grateful to Dr. Donatella Orlando for her precious help in retrieving and evaluating the literature.

## Compliance with ethical standards

**Conflict of interest** The Author declare that he has no conflict of interest.

**Statement of human and animal rights** This article does not contain any studies with human participants or animals performed by the author.

**Informed consent** Not applicable.

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