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COVID-19 PNEUMONIA: THE POINT OF VIEW OF VASCULAR SPECIALIST

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The development of coagulopathy is emerging as one of the most significant poor prognostic features in COVID-19 pneumopathy. Thromboembolic manifestations such as pulmonary embolism and disseminated intravascular coagulation (DIC) have been reported and resulted in poor prognosis for the patient.

Starting from the evidence in the literature, the purpose of this paper is to analyze potential mechanism involved in coagulation impairment following COVID-19 infection and identify possible vascular therapeutic strategies.

D-dimer, a protein product of fibrin degradation, has been found elevated in the most severe cases and correlated to mortality. Potentially involved factors in the impairment of coagulation caused by viral infection include the dysregulated inflammatory response, platelet and endothelial dysfunction with impaired fibrinolysis. Heparin is an anticoagulant molecule that also showed anti-inflammatory properties and a potential antiviral effect. A favorable outcome was highlighted with the use of LMWH in severe patients with COVID-19 who meet the SIC criteria (sepsis-induced coagulopathy) or with markedly high D-dimer. The use of low molecular weight heparin could prevent thromboembolic complications in COVID-19 pneumopathy. However, the correct timing of prophylaxis according to the stage of COVID-19 disease and the appropriate therapeutic dosage to use in severe cases need further researches.

Keywords: COVID-19, pneumonia, thrombosis, coagulopathy, D-dimer, low molecular weight heparin.

Introduction. Recent studies have shown that coagulopathy can occur during COVID-19 disease. Thromboembolic manifestations such as pulmonary embolism [1] and disseminated intravascular coagulation (DIC) [2] have been reported and resulted in poor prognosis for the patient.

Starting from the evidence in the literature, the purpose of this paper is to analyze potential mechanism involved in coagulation impairment following COVID-19 infection and identify possible vascular therapeutic strategies.

The interactions between inflammation and coagulation

A correlation between inflammation and coagulation has been widely demonstrated: inflame-

mation can lead to an altered coagulation, with a consequent imbalance between the pro- and anti-coagulant state [3]. Several inflammatory cytokines such as IL-6, IL-8, and tumor necrosis factor-alpha (TNF- α) promote a procoagulant state through the expression of the tissue factor with a mechanism that includes the activation of endothelial cells, platelets and leukocytes [4]. Furthermore, an increased release of histones and nucleosomes (DNA + histones), elements toxic to the endothelium, has been shown in sepsis and other inflammatory conditions. In contrast, activated protein C inactivates histones protecting the endothelium [5]. In response to the infection, extracellular DNA fibers extruded by neutrophils

(Neutrophil Extracellular Traps, NETs) are produced to allow neutrophils to trap and destroy invading microorganisms. NETs stimulate the formation and deposition of fibrin in order to trap microorganisms and control infection [6]. NETs also cause platelet adhesion and the link with deep vein thrombosis occurrence has been shown in some experimental models [7].

D-dimer is an epitope resulting from the plasmin degradation of cross-linked fibrin. D-dimer elevates in several conditions such as thrombosis, DIC and inflammation [8]. Notably, D-Dimer can promote the inflammatory cascade by activating neutrophils and monocytes, inducing the secretion of some inflammatory cytokines such as IL-6 [9].

Coagulation and viral infection

In several viral infections, a reduced platelet function as well as reduced platelets production or destruction has been documented phenomenon. Thrombocytopenia often occurs in both hemorrhagic and non-hemorrhagic viral infections. In most cases, thrombocytopenia is caused by autoimmune antibodies against platelets. Other mechanisms include increased platelet adhesion and activation resulting in platelet consumption and bone marrow infection that directly affects megakaryocytes and thus platelet production [3]. In SARS-CoV infection, thrombocytopenia caused by autoantibodies, presence of high levels of von Willebrand factor in the blood [10] and activation of the coagulation cascade with final generation of fibrin have been described [11]. Fibrin clots in the alveoli are an important feature of SARS-CoV infection in humans and mice. The goal of this coagulation response is probably to protect the host by sealing the alveoli, preventing edema and alveolar hemorrhages, but limiting the exchange of oxygen [12].

Markers of impaired coagulation in viral infection

A procoagulative state can be evidenced through an increase in the levels of coagulation proteins. Increased levels of fibrinogen, D-dimer, thrombin-antithrombin complexes and / or plasmin-alpha-2-antiplasmin complexes and thrombomodulin have been found in respiratory tract infections, influenza and SARS-CoV infection. Furthermore, an increase in the levels of the plasminogen-1 activator inhibitor, suggestive of impaired fibrinolysis, was also reported [3]. Recently, Tang and

collaborators reported in 15 (71.4 %) deaths for COVID-19 alterations in laboratory parameters that fulfil the diagnostic criteria of the International Society on Thrombosis and Haemostasis for DIC [2]. In particular, in the final stage of disease, the authors found high levels of D-dimer and products of the degradation of fibrinogen.

Viral infection and coagulopathy

Either bleeding or thrombosis phenomena have been described as complication in several viral infections. An exaggerated response to the infection may even lead to intravascular coagulation disseminated with the formation of microvascular thrombi in various organs [13]. Respiratory tract infections increase the risk of deep vein thrombosis and pulmonary embolism. In the H1N1 flu epidemic (swine flu), both thrombotic and hemorrhagic complications such as deep vein thrombosis, pulmonary embolism and pulmonary hemorrhage with hemoptysis, hematemesis, petechial rash, and a case of diffuse petechial cerebral hemorrhage have been reported [3]. The occurrence of disseminated intravascular coagulation, pulmonary hemorrhage and thrombocytopenia has been reported in avian influenza (H5N1) in several patients [14]. In the SARS infection induced by a coronavirus, the clinical picture related to coagulation consisted of vascular endothelial damage in small and medium-sized pulmonary vessels, disseminated intravascular coagulation, deep vein thrombosis and pulmonary thromboembolism [11].

Recently, Tang and collaborator reported a consumption coagulopathy in advanced stage of Covid-19 pneumopathy. Development of DIC results when monocytes and endothelial cells are activated to the point of cytokine release following injury, with expression of tissue factor and secretion of von Willebrand factor. Final result is circulation of free thrombin that can activate platelets and stimulate fibrinolysis [2].

Rationale for the use of heparins in Covid-19 infection

Heparins are anticoagulant drugs currently used for the prophylaxis and therapy of venous thromboembolism and are classified according to their molecular weight [15]. Heparin indirectly exerts its anticoagulant properties by binding reversibly antithrombin III (AT) amplifying its subsequent inhibitory effect on activated factor X and

thrombin (factor Xa) [16, 17]. Only UFH containing at least 18 saccharide sequences can influence the action of AT on thrombin; however, UFH fragments of any length containing a unique pentasaccharide sequence can inhibit the action of factor Xa. This feature has been exploited by pharmacological research for realization of low molecular weight heparins (LMWH) [18].

Fondaparinux, a synthetic analogue of the pentasaccharide sequence, has longer half-life than LMWH and does not interact with platelets [19]. Fondaparinux binds reversibly to AT to produce an irreversible conformational change that enhances its reactivity with factor Xa. This results in inhibition and depletion of factor Xa which in turn inhibits thrombin generation in the coagulating signal transduction pathway. Notably, this molecule is characterized by therapeutic coverage in the 24-h and non-interference with platelets. Currently, is indicated for the prophylaxis and treatment of venous thromboembolism [20].

Heparin also exhibits anti-inflammatory properties [21]. Although still to be fully clarified, some of the proposed mechanisms include binding with inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of complement factor C5a and sequestration of acute phase proteins such as P-selectin and L-selectin and induction to cell apoptosis through TNF- α and NF- κ B pathways [22, 23]. The ubiquitous endothelial cell is often affected by pathogenic invasion with consequent dysfunction. In addition, histones released from damaged cells may also be responsible for endothelial injury [5]. Heparin can antagonize histones and thus "protect" the endothelium [24, 25]. Another mechanism is through its effects on histone methylation and on the MAPK and NF- κ B signal pathways [26]. Therefore, heparin can protect from microcirculatory dysfunction and possibly decrease organ damage.

Another interesting concept is the potential antiviral role of heparin, which has been studied in experimental models. The polyanionic nature of heparin allows it to bind to different proteins and therefore act as an effective inhibitor of viral adhesion [27]. For example, in the case of herpes simplex virus infections, heparin competes with the host cell surface glycoprotein virus to limit infection and in Zika virus infection prevents cell vi-

rus-induced cell death human neural progenitors [27, 28]. Furthermore, the use of heparin at a concentration of 100 mcg/mL halved the infection in experimental cells contaminated with sputum from a patient with SARS-CoV pneumonia [29].

In a recent work, surface plasmon resonance and circular dichroism have been used and it has been shown that the binding domain of the Spike S1 SARS-CoV-2 protein receptor interacts with the heparin [30].

Finally, in the recent report by Tang and collaborators, a favorable outcome was highlighted with the use of LMWH in severe patients with COVID-19 who meet the SIC criteria (sepsis-induced coagulopathy) or with markedly high D-dimer [31, 32]. Of 99 patients treated with heparin for at least 7 days, in almost all patients (n=94) a dosage of 40/60 mg die of enoxaparin subcutaneously was used while in 5 patients unfractionated heparin was administered (10000–15000 U/day).

Considerations and possible therapeutic implications

The growing evidence puts the emphasis on an involvement of the coagulation system due to inflammation in COVID-19 pneumopathy. Although the data are still numerically insufficient to establish what the appropriate therapeutic regimen may be, the addition of heparin can have a favorable impact in COVID-19 infection disease progression. The reported data show that in most cases the infection has an asymptomatic course. The use of heparin is probably unnecessary in this population. However, in case of the onset and persistence of respiratory symptoms, even in patients in isolation at home, it is considered useful to start a prophylaxis with low molecular weight heparin (LMWH) or with Fondaparinux if renal function is preserved (creatinine clearance >50 ml/min). Should the patient develop a progressive worsening of respiratory symptoms in association with the increase in coagulation markers, therapy with LMWH should be carried out at therapeutic / sub-therapeutic doses taking into account clinical characteristics and hemorrhagic risk of patient. In advanced states, as powerful intravascular generation of thrombin occurs, unfractionated heparin could have a role. Furthermore, in these patients, careful monitoring of the coagulation parameters is necessary due to the possible evolution in DIC in the end stage of the disease [2].

Conflict of interest. The authors declare no conflict of interest.

Authors' contributions: all authors contributed to the conception and design of manuscript. LC wrote the manuscript, SAG, FPP, GA, LDP, PLA, LA, EA, GF contributed by reading and improving the manuscript.

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ПНЕВМОНИЯ ПРИ COVID-19: ВЗГЛЯД СОСУДИСТОГО ХИРУРГА

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Одним из наиболее неблагоприятных прогностических признаков пневмонии при COVID-19 является развитие коагулопатии. У пациентов с COVID-19 наблюдались признаки тромбозмболии, например тромбозмболия легочной артерии и ДВС-синдром, что негативно сказывалось на здоровье пациента.

Целью исследования является анализ потенциального механизма нарушения свертывания крови у пациентов, перенесших COVID-19, и определение возможных терапевтических стратегий.

Было обнаружено, что у пациентов с тяжелой формой заболевания уровень D-димера, белкового продукта распада фибрина, повышен и напрямую взаимосвязан со смертностью. К факторам, влияющим на нарушение коагуляции, вызванной вирусной инфекцией, относятся неуправляемый воспалительный процесс, тромбоцитарная и эндотелиальная дисфункция с нарушением фибринолиза.

Гепарин, являясь прямым антикоагулянтом, также обладает противовоспалительными свойствами и выраженным противовирусным эффектом. Благоприятный исход наблюдался при использовании низкомолекулярного гепарина у тяжелых пациентов с COVID-19 с коагулопатией, вызванной сепсисом, или высоким уровнем D-димера.

Использование низкомолекулярного гепарина может предотвратить тромбозмболические осложнения пневмонии у пациентов с COVID-19. Тем не менее точное время профилактики в зависимости от стадии заболевания COVID-19 и соответствующая терапевтическая дозировка, которая может быть использована в тяжелых случаях, требуют дальнейших исследований.

Ключевые слова: COVID-19, пневмония, тромбоз, коагулопатия, D-димер, низкомолекулярный гепарин.

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