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REVIEW PAPER

Yethindra Vityala [1], Abhijit Krishna [2], Dinesh Pandla [2], Krishna Priya Kanteti [3], Jahnavi Sadhu [4], Harsha Vardhan Boddeti [2], Tejesh Kintali [2], Mohammad Shaour Khalid [2]

Pathophysiology of thromboembolism in patients with COVID-19

[1] Department of Pathology, International Higher School of Medicine, International University of Kyrgyzstan, Bishkek, Kyrgyzstan
[2] International Higher School of Medicine, International University of Kyrgyzstan, Bishkek, Kyrgyzstan
[3] Beihua University, Jilin, China
[4] Apollo College of Physiotherapy, Telangana, India

ABSTRACT

Introduction and aim. A small number of critically ill patients with coronavirus disease (COVID-19) develop thromboembolism (arterial or venous), both micro- and macrovascular complications such as deep vein thrombosis, pulmonary embolism, and pulmonary arterial thrombosis. The objective of the study is to describe the pathophysiology of venous thromboembolism in patients with COVID-19.

Material and methods. In this article a narrative review regarding pathophysiology of thromboembolism in patients with COVID-19.

Analysis of the literature. The development of coagulopathy is a consequence of the intense inflammatory response associated with hypercoagulability, platelet activation, and endothelial dysfunction. The pathophysiology that relates pulmonary thromboembolism (PTE) with COVID-19 is associated with a hypercoagulable state. PTE is suspected in hospitalized patients presenting dyspnea, decreased oxygen requirement, hemodynamic instability, and dissociation between hemodynamic and respiratory changes. In COVID-19-associated coagulopathy, initially, patients present with elevated levels of fibrinogen and D-dimer, with minimal changes in prothrombin time and platelet count. The main risk factor for the development of pulmonary embolism is the increase in D-dimer that is associated with the development of PTE. The administration of iodine-based contrast agent to patients with COVID-19 would affect P-creatinine and renal function, where Ultrasound is viewed as cost-effective and highly portable, can be performed at the bedside.

Conclusion. Acute respiratory distress syndrome severity in patients with COVID-19 can explain PTE as a consequence of an exaggerated immune response.

Keywords. acute respiratory distress syndrome, COVID-19, pathophysiology, pulmonary embolism, thromboembolism

Corresponding author: Yethindra Vityala, e-mail: yethindravityala10@gmail.com

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in Wuhan, China, and the number of COVID-19 cases continues to increase, causing global medical, social, and economic issues.[1-3]

In severe cases, COVID-19 can be complicated by the acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury.[4] ARDS causes lung injury that occurs in response to various events and is characterized by inflammation, increased lung vascular permeability, and lung tissue with reduced aeration. Reduced lung compliance is linearly related to impaired oxygenation indicates loss of aeration leading to hypoxemia (a hallmark of ARDS pathophysiology).[5] A small number of critically ill patients with COVID-19 develop thromboembolism (arterial or venous), both micro- and macrovascular complications such as deep vein thrombosis, pulmonary embolism (PE), and pulmonary arterial thrombosis. Thromboembolic events (TEE) are a serious complication that produces an increase in morbidity and mortality.[6]

Aim

Along with the measures used to stop the spread of infections, a useful strategy was the massive acquisition and execution of diagnostic tests. The objective of the study is to describe the pathophysiology of venous thromboembolism in patients with COVID-19.

Material and methods

In this article a narrative review regarding pathophysiology of thromboembolism in patients with COVID-19.

Analysis of the literature

Etiopathogenesis of COVID-19-associated coagulopathy

The development of coagulopathy is a consequence of the intense inflammatory response associated with hypercoagulability, platelet activation, and endothelial dysfunction. Coagulopathy is mainly thrombotic, initially in the lung and later systemic, micro- and macrovascular complications associated with endothelial damage, inflammation, neutrophil extracellular traps (TENs), macrophage activation, and cytokine storm that perpetuate the vicious circle of thrombosis and inflammation (Fig. 1). The pathophysiology of thrombotic complications is complex, there are prothrombotic risk factors, including a severe inflammatory response with the production of cytokines, hypoxia, prolonged immobilization, and disseminated intravascular coagulation.[12]

Immune response

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors to infect lung cells, similarly, tissue damage occurs in endothelial cells, releasing cytokines, interleukin IL-1, IL-2, IL-6, and tumor necrosis factor-alpha that activate the coagulation cascade. During the early stage of COVID-19, ACE2 decreases followed by an increase in plasma angiotensin 2 increases, which in turn leads to vasoconstriction, platelet activation, and cytokine release syndrome.[13] ACE2 expression is predominantly seen in pneumocytes, in the endothelium,

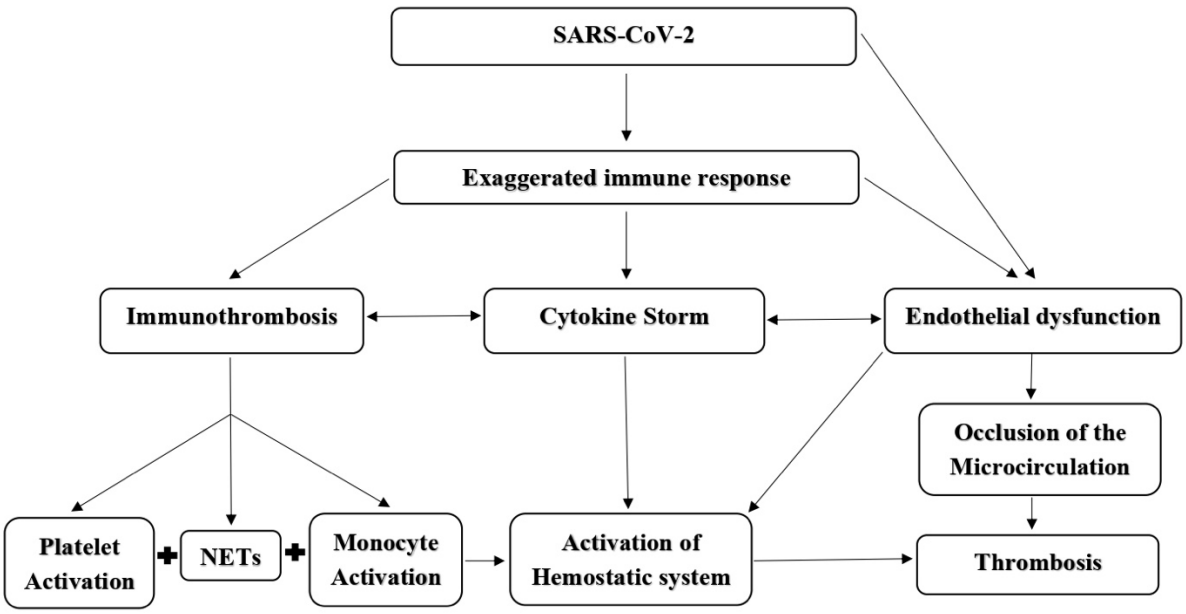

Fig. 1. Schematic representation of the mechanism responsible for the activation of the hemostatic system and thrombosis after SARS-CoV2 infection

and macrophages, apart from lung ACE2 expression are also observed in respiratory epithelial cells, enterocytes, and smooth muscle cells.[14]

SARS-CoV-2 penetrates alveolar epithelial cells through the ACE2 receptor. Viral replication triggers complement activation, with the formation of C3a and C5a, including neutrophils, macrophages, lymphocytes, and monocytes, responsible in turn for the massive release of IL1, IL-6, IL-8, and interferons that favor the tissue factor and thrombomodulin expression and endothelial adhesion molecules, which activates fibrinolysis.[15] The increased expression of tissue factor and thrombomodulin is responsible for the activation of the hemostatic system. An endothelial and platelet activation causes an imbalance between thrombin with fibrin deposition, microangiopathy, and tissue damage.

Thrombosis

Thrombosis is a hemostatic response that leads to the formation of thrombi that obstruct blood flow. An embolism occurs when the clot breaks from the site of origination, travels through the bloodstream, and blocks a blood vessel in another tissue or organ. The alpha-granules of activated platelets release platelet factor 4, attracts and activates neutrophils leading to the formation of NETs and followed by leukocyte-platelet aggregates.[16]

COVID-19 and thromboembolism

COVID-19 predisposes to venous thromboembolism (VTE) with pulmonary thromboembolism (PTE) and reported in autopsies of patients with COVID-19.[16] PTE occurs between 9-12 days after the onset of symptoms and even 23% of patients received thromboprophylaxis developed PTE. So far, there is no evidence linking the development of PE and longer intubation time in critically ill patients with COVID-19.[18] The pathophysiology that relates PTE with COVID-19 is associated with a hypercoagulable state. The systemic inflammatory response syndrome and endothelial dysfunction is associated with activation of coagulation, increased thrombin generation, and decreased anticoagulation. In 11.6% of hospitalized patients with COVID-19 despite thromboprophylaxis, VTE is reported and increased to 15.7% in hospitalized patients with COVID-19 admitted to the intensive care unit.[19] The prevalence of PTE in patients with COVID-19 is 16% higher than in those patients without COVID-19.[20] PTE is suspected in hospitalized patients presenting dyspnea, decreased oxygen requirement, hemodynamic instability, and dissociation between hemodynamic and respiratory changes.

Pathogenesis of COVID-19-associated coagulopathy

In COVID-19-associated coagulopathy, initially, patients present with elevated levels of fibrinogen and D-dimer, with minimal changes in prothrombin time and platelet count. Coagulopathy can be diagnosed by increased D-dimer, elevated levels of fibrinogen (initially fibrinogen increases in the acute phase and later decreases to <100 mg/dL in patients with poor prognosis). Prothrombin time, partial thromboplastin time, and platelet count are within normal limits.[21] The main risk factor for the development of PE is the increase in D-dimer and an increase in D-dimer >6 μg/mL is associated with the development of PTE with an OR 4.8 (CI 3.2-7.2). The elevation of D-dimer is associated with a disease progression from mild or moderate stage to a more severe disease stage, with intensive care unit admission and an increase in mortality due to the fibrinolysis in the airway and the alveoli of the lung. In this extravascular fibrinolysis, inflammatory cells invade lung tissue because of fibrin deterioration and increased D-dimer levels, which justifies the correlation with the severity of the lung disease and not only due to TEE. The concentration of D-dimer, a protein fragment present in the blood resulting from clot degradation that is commonly found in patients with the suspected thrombotic disorder and significantly increased in the patients with ARDS.[22]

Non-hospitalized immobilized patients with COVID-19 had a cumulative effect on TEE risk but hospitalization can also lead to TEE and PE in non-immobilized patients.

Computerized axial tomography scan

Computed Tomography (CT) pulmonary angiogram is the investigation of choice in patients with suspected PE because it allows adequate visualization of the pulmonary arteries till the subsegmental sections (Fig. 2).

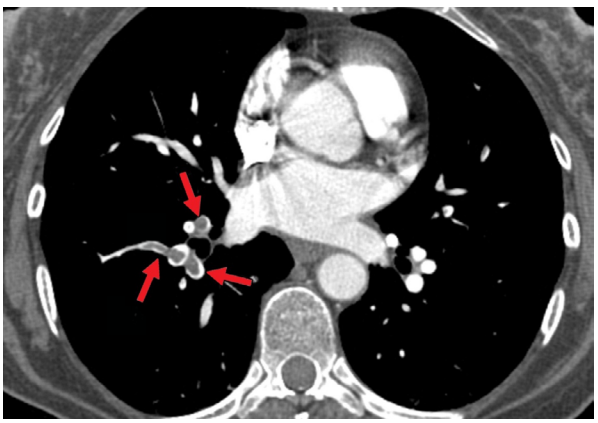

Fig. 2. Computed Tomography pulmonary angiogram showing acute pulmonary embolism (red arrows) in right lower lobe pulmonary arteries

Most number of emboli were observed in segmental section (51%), lobar (31%), central (13%) and subsegmental 5.5%.[23] CT has 83% sensitivity and 96% specificity for the diagnosis of PE and showed a high

negative predictive value of CT angiography. The administration of iodine-based contrast agent to patients with COVID-19 would affect P-creatinine and renal function. Moreover, critically ill patients with COVID-19 are at increased risk of contrast-induced acute kidney injury but acute kidney injury was not associated with the administration of iodinated contrast material.[24] Compared to CT, Ultrasound is viewed as cost-effective and highly portable, can be performed at the bedside, therefore a promising alternative to address these requirements.[25] Currently, extremity venous Doppler ultrasound for deep vein thrombosis is recommended for symptomatic patients and bedside echocardiography helps diagnose PE-associated findings (right ventricular dilatation or dysfunction and intracardiac thrombus), indicating a clot-in-transit.[26]

Conclusion

ARDS severity in patients with COVID-19 can explain PTE as a consequence of an exaggerated immune response.

Declarations

Funding

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Author contributions

Conceptualization, Y.V., A.K., D.P., K.P.K. and J.S.; Formal Analysis, K.P.K., J.S., H.V.B., T.K. and M.S.K.; Writing – Review & Editing, Y.V., A.K., D.P., K.P.K., J.S., H.V.B., T.K., and M.S.K.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

Data are available from the corresponding author upon reasonable request.

References

1. Bassetti M, Vena A, Giacobbe DR. The novel Chinese coronavirus (2019-nCoV) infections: challenges for fighting the storm. *Eur J Clin Invest*. 2020;50:e13209.
2. CDC. About COVID-19. Centers for Disease Control and Prevention; 2019. Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html. Accessed: 2020 Dec 08.
3. WHO. Coronavirus. World Health Organization; 2019. Available from: https://www.who.int/health-topics/coronavirus. Accessed: 2021 Dec 08.
4. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
5. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis*. 1987;136(3):730-736.
6. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis*. 2020;20(10):1135-1140.
7. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69(6):1002-1009.
8. Espy MJ, Uhl JR, Sloan LM, et al. Real-time PCR in clinical microbiology: applications for routine laboratory testing. *Clin Microbiol Rev*. 2006;19(1):165-256.
9. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill*. 2020;25(3):2000045.
10. Corman VM, Müller MA, Costabel U, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. *Euro Surveill*. 2012;17(49):20334.
11. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323(18):1843-1844.
12. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect*. 2020;53(3):368-370.
13. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033-2040.
14. Bertram S, Heurich A, Lavender H, et al. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. *PLoS One*. 2012;7(4):e35876.
15. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol*. 2020;215:108427.
16. Middleton EA, He XY, Denorme F, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. 2020;136(10):1169-1179.
17. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746.
18. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. *Thromb Res*. 2020;192:152-160.
19. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424.
20. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
21. López-Reyes R, Oscullo G, Jiménez D, Cano I, García-Ortega A. Thrombotic Risk and Covid-19: Review of Current Evidence for a Better Diagnostic and Therapeutic Approach. *Arch Bronconeumol*. 2021;57:55-64.

22. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-128.
23. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected with Pulmonary CT Angiography. *Radiology*. 2020;296(3):186-188.
24. Mathews BK, Koenig S, Kurian L, et al. Clinical Progress Note: Point-of-Care Ultrasound Applications in COVID-19. *J Hosp Med*. 2020;15(6):353-355.
25. Lu W, Zhang S, Chen B et al. A Clinical Study of Noninvasive Assessment of Lung Lesions in Patients with Coronavirus Disease-19 (COVID-19) by Bedside Ultrasound. *Ultraschall Med.* 2020;41(03):300-307.
26. Gogna A, Yogendra P, Lee SHE, et al. Diagnostic ultrasound services during the coronavirus disease (COVID-19) pandemic. *Am J Roentgenol*. 2020;215(5):1130-1135.