EDITORIAL

JORNAL VASCULAR BRASILEIRO
ISSN 1677-7301 (Online)

Physiopathology of SARS-CoV-2-infection-associated thrombosis

Fisiopatologia da trombose associada à infecção pelo SARS-CoV-2

Ivan Benaduce Casella[1]

How to cite: Casella IB. Physiopathology of SARS-CoV-2-infection-associated thrombosis. J Vasc Bras. 2020;19:e20200128. https://doi.org/10.1590/1677-5449.200128

The pandemic provoked by the novel coronavirus (SARS-CoV-2) is the most severe public health event of recent decades, with more than 11.1 million cases registered worldwide up to the start of July 2020 and more than 528 thousand deaths.[1] There are many different clinical manifestations of infection by SARS-CoV-2 and the pathophysiologic processes that provoke them are also numerous and varied. Since the early stages of the pandemic, the number of thrombotic events of varying types has attracted the attention of physicians and researchers, invoking the need to understand them in order to avert the most somber of clinical outcomes.

The modest ambition of this editorial is to present the scientific theories and evidence on the pathophysiology of thrombotic processes associated with infection by SARS-CoV-2. However, certain important provisos should be made clear: part of these scientific explanations have not yet progressed beyond the status of hypotheses; the pathological processes observed rather than sequential, are predominantly concomitant and stimulate each other; it is difficult to quantify the impact of events that take place on the molecular and cellular scales have on the final clinical outcomes of the thrombotic event.

THE ROLE OF ANGIOTENSIN-CONVERTING ENZYME TYPE 2 (ACE2)

The principal mechanism that SARS-CoV-2 has for accessing the intracellular environment is through interaction between its S surface glycoprotein and the human ACE2 glycoprotein, which is present both in plasma and in the membranes of several different cell types.[2] ACE2 acts as a membrane receptor in this process, which also involves interactions with other effectors, such as type 2 transmembrane serine proteases.[3]

The ACE2 protein plays an important role as a negative effector in the renin angiotensin aldosterone system, converting angiotensins I and II into angiotensins 1-9 and 1-7, respectively. Angiotensins 1-9 and 1-7 have vasodilatory and anti-inflammatory effects, among other actions, thereby antagonizing the classic hypertensive and inflammatory effects of angiotensin II.[2,3]

Infection by SARS-CoV-2 causes death of cells rich in ACE2 receptors and cellular internalization of a proportion of these receptors, ultimately causing a reduction in circulating ACE2 activity.[4] This results in angiotensin II activity predominating over activity of angiotensins 1-7 and 1-9. In addition to its hypertensive and inflammatory effects, angiotensin II stimulates activation of the coagulation cascade via the tissue factor (TF) pathway, elevates activity of tissue plasminogen activator inhibitor type 1 (PAI-1) and inhibits expression of tissue plasminogen activator (tPA).[5]

IMMUNOTHROMBOSIS AND NEUTROPHIL EXTRACELLULAR TRAPS

The term "immunothrombosis" has been used to describe the interactions between macrophages, polymorphonuclear cells, platelets, coagulation factors, and immunoeffector proteins, forming thrombi in the microvasculature which function to recognize pathogens and mechanically preventing them from propagating.[6] Immunothrombosis is usually triggered by infectious agents circulating in the blood and can be activated by viral infections.

The polymorphonuclear cells involved in this process stimulate formation of neutrophil extracellular traps, which can stimulate coagulation activation via factor XII and also act to inhibit endogenous anticoagulant proteins.[5] Zuo et al. observed that

[1] Universidade de São Paulo – USP, Faculdade de Medicina, Hospital das Clínicas, São Paulo, SP, Brasil.
Financial support: None.
Conflicts of interest: No conflicts of interest declared concerning the publication of this article.
Submitted: July 20, 2020. Accepted: July 22, 2020.

elevated levels of neutrophil activation and formation of neutrophil extracellular traps in patients positive for Covid (Covid+) were associated with an increased risk of thrombotic complications.[7]

ENDOTHELIAL RESPONSE, INFLAMMATION, AND THROMBOSIS

Ackermann et al.[8] demonstrated that pulmonary infection by SARS-CoV-2 is associated with microthrombosis, endotheliitis, and intussusceptive angiogenesis, at an intensity not observed in other viral infections or interstitial pneumonia of similar severity. Under physiological conditions, the vascular endothelium has a variety of different mechanisms for inhibiting thrombotic events. Conversely, pathological stimuli at the cellular or molecular level stimulate thrombogenic endothelial responses, such as increased expression of FT and of PAI-1, platelet activation, release of inflammatory cytokines and reduced expression of endogenous anticoagulants, such as thrombomodulin.[9]

These inflammatory cytokines are also massively secreted by alveolar macrophages and epithelial and polymorphonuclear cells[10] provoked by the exaggerated interferon-mediated late immune response.[11] The vicious circle of inflammation and thrombosis is reignited by cytokines, which are chemotactic factors for leukocytes, activate coagulation via tissue factor, inhibit fibrinolysis by increasing expression of PAI-1, and inhibit endogenous anticoagulant pathways, such as antithrombin, protein C, and its cofactor, protein S.[10,12]

The complement system is an element in the immune response to SARS-CoV-2 infection and is also associated with the thrombotic processes observed. Magro et al.[13] observed intense complement system activity in critical patients who were positive for SARS-CoV-2, with deposition of C5b-9 and C4d fractions in the microvasculature, associated with microthrombosis with deposition of fibrin and endothelial injury.

D DIMER

Marked D dimer elevation has been observed in Covid+ patients, with extremely high levels in the most severe patients and clear associations with poor prognosis.[14] While the phenomenon is not entirely understood, it may be related to occurrence of massive microvascular thrombosis and activation of the fibrinolytic system by direct viral stimulation, followed by thrombolysis inhibition.[14,15]

In summary, we can group the effects of the events described into four main results that act on coagulation: (1) activation of the coagulation cascade by different routes and multiple stimuli of different origins; (2) platelet activation; (3) inhibition of endogenous anticoagulant proteins (protein C and its cofactor protein S, antithrombin, and tissue factor pathway inhibitor); and (4) inhibition of the fibrinolytic system (fibrinolysis shutdown).

SARS-COV-2 INFECTION, THROMBOTIC EVENTS, AND HEPARIN RESISTANCE

Several authors[16-18] have reported increased rates of thrombotic events, in both the venous (deep venous thrombosis and pulmonary embolism) and arterial systems (ischemic strokes and peripheral arterial thromboses) of patients infected by SARS-CoV-2. The methods used in these reports differ considerably, preventing compilation of homogenous data. Helms et al.[19] observed increased incidence of venous thromboembolism in critical patients infected by SARS-CoV-2 in comparison with patients with severe respiratory infections caused by other pathogens.

White et al.[20] observed a small cohort of patients infected by SARS-CoV-2 who were given therapeutic anticoagulation with heparins. In this group, 5 out of 5 patients treated with enoxaparin exhibited lower anti-factor Xa activity than required for the drug to have therapeutic effects. With unfractionated heparin, 8 out of 10 patients exhibited resistance to anticoagulation.

In a similar manner, Dutt et al.[21] noted that 27% of patients with non-severe SARS-CoV-2 infection who were given prophylactic doses of heparin had anti-factor Xa activity below the level indicative of prophylaxis efficacy. Among the more serious patients, in intensive care, the percentage was 95%.

CONCLUSIONS

Current evidence indicates that there is an elevated incidence of clinically relevant thrombotic events is associated with SARS-CoV-2 infection. Understanding of the pathophysiologic processes that cause these thrombotic phenomena is still incomplete. The cause-effect relationship between thrombotic events and the severity of SARS-CoV-2 infection also needs to better understood. It is not clear whether it is patients with greater thrombotic response who have more severe clinical presentations, or whether the process follows the opposite sequence, by which cases of greater clinical severity have a higher incidence of thrombotic events.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19): Situation Report – 167. Geneva: WHO; 2020 [cited 2020 July 20]. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200705-covid-19-sitrep-167.pdf?sfvrsn=17e7e3df_4
2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8. http://dx.doi.org/10.1016/j.cell.2020.02.052. PMid:32142651.
3. Xiao L, Sakagami H, Miwa N. ACE2: the key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: Demon or Angel? Viruses. 2020;12(5):491. http://dx.doi.org/10.3390/v12050491. PMid:32354022.
4. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-74. http://dx.doi.org/10.1161/CIRCRESAHA.120.317015. PMid:32264791.
5. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta. 2020;507:167-73. http://dx.doi.org/10.1016/j.cca.2020.04.027. PMid:32348783.
6. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013;13(1):34-45. http://dx.doi.org/10.1038/nri3345. PMid:23222502.
7. Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. medRxiv. 2020 May 5. Epub ahead of print. http://dx.doi.org/10.1101/2020.04.30.20086736. PMid:32511553.
8. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8. http://dx.doi.org/10.1056/NEJMoa2015432. PMid:32437596.
9. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133(9):906-18. http://dx.doi.org/10.1182/blood-2018-11-882993. PMid:30642917.
10. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-74. http://dx.doi.org/10.1038/s41577-020-0311-8. PMid:32346093.
11. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev. 2020;19(6):102537. http://dx.doi.org/10.1016/j.autrev.2020.102537. PMid:32251717.
12. Levi M, van der Poll T, ten Cate H, van Deventer SJ. The cytokine-mediated imbalance between coagulant and anticoagulant mechanisms in sepsis and endotoxaemia. Eur J Clin Invest. 1997;27(1):3-9. http://dx.doi.org/10.1046/j.1365-2362.1997.570614.x. PMid:9041370.
13. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020;220:1-13. http://dx.doi.org/10.1016/j.trsl.2020.04.007. PMid:32299776.
14. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. http://dx.doi.org/10.1111/jth.14768. PMid:32073213.
15. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg. 2020:231(2):203-4. https://doi.org/10.1016/j.jamcollsurg.2020.05.007.
16. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. 2020;191:148-50. http://dx.doi.org/10.1016/j.thromres.2020.04.041. PMid:32381264.
17. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002. http://dx.doi.org/10.1111/jth.14888. PMid:32369666.
18. Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020:142(2):114-28. https://doi.org/10.1161/CIRCULATIONAHA.120.046702.
19. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. http://dx.doi.org/10.1007/s00134-020-06062-x. PMid:32367170.
20. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis. 2020;50(2):287-91. PMid:32445064.
21. Dutt T, Simcox D, Downey C, et al. Thromboprophylaxis in COVID-19: Anti-FXa - The Missing Factor? Am J Respir Crit Care Med. 2020;202(3):455-7. http://dx.doi.org/10.1164/rccm.202005-1654LE. PMid:32510975.

Correspondence
Ivan Benaduce Casella
Universidade de São Paulo – USP, Instituto Central, Faculdade de Medicina – FM, Hospital das Clínicas – HC, Disciplina de Cirurgia Vascular e Endovascular
Rua Ovídio Pires de Campos, s/n, 6º andar, PAMB, bloco 5, Cerqueira César
CEP 05403-911 - São Paulo (SP), Brasil
Tel.: +55 (11) 2661-6101
E-mail: ivan.c@hc.fm.usp.br

Author information
IBC - Vascular surgeon, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (FMUSP).

EDITORIAL

JORNAL VASCULAR BRASILEIRO
ISSN 1677-7301 (Online)

Fisiopatologia da trombose associada à infecção pelo SARS-CoV-2

Physiopathology of SARS-CoV-2-infection-associated thrombosis

Ivan Benaduce Casella[1]

Como citar: Casella IB. Fisiopatologia da trombose associada à infecção pelo SARS-CoV-2. J Vasc Bras. 2020;19:e20200128. https://doi.org/10.1590/1677-5449.200128

A pandemia provocada pelo novo coronavírus (SARS-CoV-2) é o evento mais severo de saúde pública das últimas décadas, com mais de 11,1 milhões de casos contabilizados em todo o mundo até o início de julho de 2020 e mais de 528 mil mortes[1]. As manifestações clínicas da infecção pelo SARS-CoV-2 são múltiplas, assim como os processos fisiopatológicos que as proporcionam. Desde o início, o número de eventos trombóticos de diversas naturezas tem chamado a atenção de médicos e pesquisadores, evocando a necessidade de sua compreensão para que os desfechos clínicos mais sombrios sejam evitados.

Este editorial tem a modesta pretensão de apresentar as teorias e evidências científicas acerca da fisiopatologia dos processos trombóticos associados à infecção pelo SARS-CoV-2. No entanto, há alguns aspectos importantes a serem realçados: parte das explicações cientificas ainda se encontram no campo das hipóteses; os processos patológicos observados são predominantemente concomitantes e se estimulam mutuamente; ainda é difícil quantificar o impacto isolado de eventos que ocorrem em escala molecular e celular nos desfechos clínicos finais do evento trombótico.

PAPEL DA ENZIMA DE CONVERSÃO DA ANGIOTENSINA TIPO 2 (ECA2)

O principal mecanismo de acesso do SARS-CoV-2 ao meio intracelular se dá pela interação de sua glicoproteína de superfície S com a glicoproteína humana ECA2, presente tanto no plasma como na membrana de diversos tipos celulares[2]. Nesse processo, a ECA2 atua como receptor de membrana, contando ainda com a interação de outros efetores, como a serina protease transmembrana tipo 2[3].

A proteína ECA2 cumpre importante papel de efetor negativo no sistema renina angiotensina aldosterona, convertendo as angiotensinas I e II em angiotensinas 1-9 e 1-7, respectivamente. As angiotensinas 1-9 e 1-7 apresentam efeitos vasodilatadores e anti-inflamatórios, dentre outros, antagonizando, assim, os efeitos clássicos hipertensivos e inflamatórios da angiotensina II[2,3].

A infecção pelo SARS-CoV-2 resulta em morte de células ricas em receptores ECA2 e na internalização celular de parte desses receptores, causando, em última instância, redução da atividade da ECA2 circulante[4]. Com isso, há um predomínio da atividade da angiotensina II sobre as angiotensinas 1-7 e 1-9. A angiotensina II, além de seu efeito hipertensor e inflamatório, estimula a ativação da cascata da coagulação pela via do fator tissular (FT), eleva a atividade do inibidor do ativador do plasminogênio tecidual tipo 1 (PAI-1) e inibe a expressão do ativador do plasminogênio tecidual (tPA)[5].

IMUNOTROMBOSE E REDES EXTRACELULARES DE NEUTRÓFILOS

O termo "imunotrombose" tem sido utilizado para descrever a interação entre macrófagos, polimorfonucleares, plaquetas, fatores de coagulação e proteínas imunoefetoras, formando trombos na microvasculatura com o intuito de identificar patógenos e restringir mecanicamente a sua propagação[6]. A imunotrombose é usualmente desencadeada por agentes infecciosos circulantes no sangue, podendo também ser acionada em infecções virais.

Os polimorfonucleares envolvidos nesse processo estimulam a formação de redes extracelulares de neutrófilos, que podem estimular a ativação da coagulação via fator XII atuando também na inibição de proteínas anticoagulantes endógenas[5]. Zuo et al. observaram que elevados níveis de ativação de neutrófilos e formação de redes extracelulares de neutrófilos em pacientes

[1] Universidade de São Paulo – USP, Faculdade de Medicina, Hospital das Clínicas, São Paulo, SP, Brasil.
Fonte de financiamento: Nenhuma.
Conflito de interesse: O autor declarou não haver conflitos de interesse que precisam ser informados.
Submetido em: Julho 20, 2020. Aceito em: Julho 22, 2020.

positivos para Covid (Covid+) foram associados a maior risco de complicações trombóticas[7].

RESPOSTA ENDOTELIAL, INFLAMAÇÃO E TROMBOSE

Ackermann et al.[8] demonstraram que infecção pulmonar pelo SARS-CoV-2 está associada a microtrombose, endotelite e angiogênese intussusceptiva, em uma intensidade não observada em outras infecções virais ou pneumonias intersticiais de semelhante gravidade. O endotélio vascular em condições fisiológicas dispõe de diversos mecanismos inibidores de eventos trombóticos. De forma oposta, estímulos patológicos em nível celular ou molecular estimulam uma resposta trombogênica endotelial, como o aumento da expressão do FT e do PAI-1, ativação plaquetária, liberação de citocinas inflamatórias e redução de expressão de anticoagulantes endógenos, como a trombomodulina[9].

Essas citocinas inflamatórias também são maciçamente liberadas por macrófagos alveolares, células epiteliais e polimorfonucleares[10] pela resposta imunológica tardia e exacerbada mediada por interferons[11]. Realimentando o círculo vicioso da inflamação e trombose, as citocinas são fatores quimiotáticos para leucócitos, ativam a coagulação pela via do fator tissular, inibem a fibrinólise ao elevar a expressão do PAI-1 e inibem vias anticoagulantes endógenas, como a antitrombina, a proteína C e seu cofator, a proteína S[10,12].

O sistema complemento é um dos elementos da resposta imune na infecção pelo SARS-CoV-2 e também está associado aos processos trombóticos observados. Magro et al.[13] observaram intensa atividade do sistema complemento em pacientes críticos positivos para SARS-CoV-2, com deposição de frações C5b-9 e C4d na microvasculatura, associadas à microtrombose com deposição de fibrina e lesão endotelial.

DÍMERO D

A marcante elevação do dímero D foi observada em pacientes Covid+, sendo superlativa nos pacientes mais graves e claramente associada a piores prognósticos[14]. Embora não totalmente compreendida, pode ser explicada pela ocorrência de maciça trombose microvascular e pela ativação do sistema fibrinolítico por estímulo viral direto com posterior inibição deste[14,15].

Resumidamente, podemos agrupar os efeitos dos eventos descritos em quatro resultantes principais agindo sobre a coagulação: (1) ativação da cascata da coagulação por vias distintas e múltiplos estímulos de origens distintas; (2) ativação plaquetária; (3) inibição das proteínas anticoagulantes endógenas (proteína C e seu cofator proteína S, antitrombina, inibidor da via do fator tissular); (4) inibição do sistema fibrinolítico ("*fibrinolysis shutdown*").

INFECÇÃO PELO SARS-COV-2, EVENTOS TROMBÓTICOS E RESISTÊNCIA À HEPARINA

Diversos autores[16-18] reportaram aumento de eventos trombóticos tanto venosos (trombose venosa profunda, embolia pulmonar) quanto arteriais (acidente vascular encefálico isquêmico, tromboses arteriais periféricas) em pacientes infectados pelo SARS-CoV-2. Tais relatos diferem bastante em seus métodos, o que impede a obtenção de dados homogêneos. Helms et al.[19] observaram incidência aumentada de eventos de tromboembolismo venoso em pacientes graves infectados pelo SARS-CoV-2 em comparação com pacientes com infecções respiratórias severas causadas por outros patógenos.

White et al.[20] observaram um pequeno coorte de pacientes infectados pelo SARS-CoV-2 recebendo anticoagulação terapêutica com heparinas. Neste grupo, 5 em 5 pacientes tratados com enoxaparina apresentaram níveis de atividade antifator Xa inferiores aos esperados para ação terapêutica da droga. Para a heparina não fracionada, 8 em 10 pacientes apresentaram resistência à anticoagulação.

De maneira similar, Dutt et al.[21] notaram que 27% dos pacientes com infecção não severa pelo SARS-CoV-2 recebendo doses profiláticas de heparina apresentavam valores de atividade antifator Xa abaixo dos níveis indicadores de efetividade da profilaxia. Já nos pacientes mais graves, internados em ambiente de terapia intensiva, a porcentagem era de 95%.

CONCLUSÕES

As evidências atuais indicam que existe uma expressiva incidência de eventos trombóticos clinicamente relevantes associados à infecção pelo SARS-CoV-2. A compreensão dos processos fisiopatológicos que resultam em tais fenômenos trombóticos ainda é incompleta. Também, a relação de causa e efeito entre eventos trombóticos e a gravidade da infecção pelo SARS-CoV-2 ainda precisa ser mais bem compreendida. Não está claro se são os pacientes com maior resposta trombótica que apresentam os quadros clínicos mais severos ou se o processo é sequencialmente oposto, em que os casos clinicamente mais graves resultam em maior incidência de eventos trombóticos.

REFERÊNCIAS

1. World Health Organization. Coronavirus disease (COVID-19): Situation Report – 167. Geneva: WHO; 2020 [cited 2020 July 20].

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200705-covid-19-sitrep-167.pdf?sfvrsn=17e7e3df_4

2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.e8. http://dx.doi.org/10.1016/j.cell.2020.02.052. PMid:32142651.
3. Xiao L, Sakagami H, Miwa N. ACE2: the key molecule for understanding the pathophysiology of severe and critical conditions of COVID-19: Demon or Angel? Viruses. 2020;12(5):491. http://dx.doi.org/10.3390/v12050491. PMid:32354022.
4. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-74. http://dx.doi.org/10.1161/CIRCRESAHA.120.317015. PMid:32264791.
5. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta. 2020;507:167-73. http://dx.doi.org/10.1016/j.cca.2020.04.027. PMid:32348783.
6. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013;13(1):34-45. http://dx.doi.org/10.1038/nri3345. PMid:23222502.
7. Zuo Y, Zuo M, Yalavarthi S, et al. Neutrophil extracellular traps and thrombosis in COVID-19. medRxiv. 2020 May 5. Epub ahead of print. http://dx.doi.org/10.1101/2020.04.30.20086736. PMid:32511553.
8. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8. http://dx.doi.org/10.1056/NEJMoa2015432. PMid:32437596.
9. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133(9):906-18. http://dx.doi.org/10.1182/blood-2018-11-882993. PMid:30642917.
10. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-74. http://dx.doi.org/10.1038/s41577-020-0311-8. PMid:32346093.
11. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmun Rev. 2020;19(6):102537. http://dx.doi.org/10.1016/j.autrev.2020.102537. PMid:32251717.
12. Levi M, van der Poll T, ten Cate H, van Deventer SJ. The cytokine-mediated imbalance between coagulant and anticoagulant mechanisms in sepsis and endotoxaemia. Eur J Clin Invest. 1997;27(1):3-9. http://dx.doi.org/10.1046/j.1365-2362.1997.570614.x. PMid:9041370.
13. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020;220:1-13. http://dx.doi.org/10.1016/j.trsl.2020.04.007. PMid:32299776.
14. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. http://dx.doi.org/10.1111/jth.14768. PMid:32073213.
15. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg. 2020:231(2):203-4. https://doi.org/10.1016/j.jamcollsurg.2020.05.007.
16. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. 2020;191:148-50. http://dx.doi.org/10.1016/j.thromres.2020.04.041. PMid:32381264.
17. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002. http://dx.doi.org/10.1111/jth.14888. PMid:32369666.
18. Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020:142(2):114-28. https://doi.org/10.1161/CIRCULATIONAHA.120.046702.
19. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. http://dx.doi.org/10.1007/s00134-020-06062-x. PMid:32367170.
20. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis. 2020;50(2):287-91. PMid:32445064.
21. Dutt T, Simcox D, Downey C, et al. Thromboprophylaxis in COVID-19: Anti-FXa - The Missing Factor? Am J Respir Crit Care Med. 2020;202(3):455-7. http://dx.doi.org/10.1164/rccm.202005-1654LE. PMid:32510975.

Correspondência
Ivan Benaduce Casella
Universidade de São Paulo – USP, Instituto Central, Faculdade de Medicina – FM, Hospital das Clínicas – HC, Disciplina de Cirurgia Vascular e Endovascular
Rua Ovídio Pires de Campos, s/n, 6º andar, PAMB, bloco 5, Cerqueira César
CEP 05403-911 - São Paulo (SP), Brasil
Tel.: (11) 2661-6101
E-mail: ivan.c@hc.fm.usp.br

Informações sobre o autor
IBC - Cirurgião vascular, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (FMUSP).