Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Trends in Cardiovascular Medicine 31 (2021) 161–162

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial commentary: Understanding thrombosis in COVID-19 – A long way to go ☆

Fizzah A Choudry [a,b], Anthony Mathur [a,b], Daniel A Jones [a,b,*]

[a] Department of Cardiology, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, United Kingdom
[b] Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, United Kingdom

COVID-19 results in a number of coagulation abnormalities including raised D-dimer, prolonged prothrombin time and thrombocytopaenia which are believed to lead to thrombotic complications [1,2]. Consequently, venous and arterial thromboembolism have been reported and whilst the true incidence of thromboembolic disease is unknown, data from case series suggest that thrombotic complications of COVID-19 are common [3–7]. Reported rates of thrombotic complications are high with 25% incidence of venous thromboembolism reported among 81 intensive care patients in Wuhan, China [4] and 31% cumulative incidence of venous or systemic arterial thrombosis including ischaemic stroke and myocardial infarction in 184 intensive care unit patients with COVID-19 in the Netherlands [7]. Subsequent studies from France and Italy have also reported high rates of thromboembolic events in critically ill patients with COVID-19 (17–22%) despite prophylactic anticoagulation [6,8,9,10]. In this issue of Trends in Cardiovascular Medicine, *Ali and Spinler* [11] have performed a timely and comprehensive review on COVID-19 and thrombosis with respect to its underlying mechanisms. The authors present proposed pathophysiological pathways for COVID-19 induced thrombosis with a particular focus on the potential for their exploitation as therapeutic targets. The authors should be congratulated on their thorough overview of the subject area with a valiant attempt to identify possible therapeutics. They coherently report cases series and studies that all appear to demonstrate an association between dysregulation of the coagulation system, elevated inflammatory markers and poor prognosis. In critically ill patients with COVID-19 the severe inflammatory response, hypoxia and direct viral mediated effects as well as the increased ACE2 expression in endothelial cells, are thought to contribute to a prothrombotic milieu and lead to the high rates of thrombotic complications. The mechanisms in this setting are detailed in this review including 1. dysregulation of the renin-angiotensin-aldosterone system leading to oxidative stress, endothelial dysfunction and activation of von Willebrand factor and 2. dysregulation of the immune response involving complement activation, neutrophil extracellular traps and mitogen activated protein kinase pathways.

Potential novel therapeutics suggested based on the mechanistic pathways described include Vitamin C aimed at oxidative stress damage, *N*-acetylcysteine aimed at breaking down large von Willebrand factor multimers that are activated upon endothelial damage, and recombinant anti-C5a antibody targeting at the complement pathway. However, for now there is no clinical evidence to support their use. In terms of current therapeutics, treatment dose anticoagulation has been suggested in critically ill patients with heparin and low molecular weight (LMW) heparin having theoretical benefits over vitamin K antagonists and direct oral anticoagulants, as they are thought to possess anti-inflammatory properties beneficial in the context of COVID-19 infection [12,13,14,15]. This is, however, only supported by observational data. In a large study of 2773 patients hospitalized with COVID-19, 786 receiving treatment dose heparin during their hospital stay showed a significantly improved survival with the mortality benefit being more marked in the 234 patients requiring mechanical ventilation [16]. While there are data from a number of cohort studies well described in the review, randomised controlled trials are underway including FREEDOM COVID (NCT04512079) randomizing 3600 1:1:1 to prophylactic LMW heparin, treatment dose LMW heparin or apixaban. Such studies will guide the future use of current pharmacotherapies. However, disturbingly there have been reports of heparin resistance in COVID-19 [17] and in the setting of ST elevation myocardial infarction (STEMI) higher doses of heparin are needed to achieve therapeutic activated clotting times [18]. Aside from anticoagulation, a New York case series has demonstrated the therapeutic benefit of tissue plasminogen activator in COVID-19 patients with refractory respiratory failure on mechanical ventilation which also suggests that pulmonary microvascular thrombi may in part drive the pathophysiology of certain phenotypes of acute respiratory distress syndromes in COVID-19 [19,20].

Venous thromboembolism forms the main focus of the review by *Ali and Spinler* with most of the evidence cited coming from series and studies in critically ill patients, suggesting the increased pre-disposition appearing to be associated with severe forms of COVID-19. It is interesting to note that there is now mounting evidence for thromboembolism, particularly arterial as the first manifestation of COVID-19 infection. A case series from New York reported on a high incidence of young pa-

☆ All authors: No conflicts of interest, nothing to disclose.
DOI of original article: 10.1016/j.tcm.2020.12.004

* Corresponding author at: Department of Cardiology, Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, United Kingdom.
E-mail address: dan.jones8@nhs.net (D.A. Jones).

https://doi.org/10.1016/j.tcm.2020.12.006

tients presenting with large vessel occlusion and ischaemic stroke as a first presentation of COVID-19 [21]. Similarly, an Italian series has reported increased incidence of acute limb ischaemia presentation in COVID-19 [22]. Furthermore, in a large series from London of COVID-19 patients presenting with STEMI, the majority of cases acute coronary thrombosis was the first presentation of infection suggesting that COVID-19 can cause acute arterial thrombosis even in the absence of substantial systemic inflammation. Furthermore, when compared to STEMI cases without concurrent COVID-19 there were unique features of the percutaneous coronary intervention (PCI) procedure that demonstrated a strong signal towards higher thrombus burden than usual including higher rates of multivessel thrombosis, stent thrombosis and higher modified thrombus grade post first device intervention [18]. It remains unclear however what the underlying mechanism would be although direct endothelial or vascular injury might be a major contributory factor [23] and targeted inhibition of endothelial infection may offer unique opportunities to prevent and treat COVID-19 infection [24].

This timely comprehensive review by *Ali and Spinler* with the world in the midst of the second wave of COVID-19 highlights the need for further work into novel therapeutic options based on the postulated mechanisms underlying the problem of thrombosis in COVID-19 patients. We would suggest that these mechanisms may vary with venous or arterial thromboembolism. The mechanistic distinction between venous thromboembolism in systemically unwell COVID-19 patients and atrial thrombosis as a first presentation of COVID-19 is yet to be elucidated. In terms of current therapeutics, we await the results of ongoing trials of anticoagulation in this patient cohort.

References

[1] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.

[2] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094–9.

[3] Casey K, Iteen A, Nicolini R, Auten J. COVID-19 pneumonia with hemoptysis: acute segmental pulmonary emboli associated with novel coronavirus infection. Am J Emerg Med 2020;38 1544.e1-1544.e3.

[4] 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;18:1421–4.

[5] Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association. Eur Heart J 2020;41:1858.

[6] Helms J, Tacquard C, Severac F, Leonard- Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089–98.

[7] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gammers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.

[8] Llitjos JF, Leclerc M, Chochois C, Monsallier J-M, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18:1743–6.

[9] Lodigiani C, Iapichino G, Carenzo Cecconi M, Ferazzi P, Sebastian T, 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.

[10] Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. Intensive Care Med 2020;46(6):1121–3.

[11] Ali MAM, Spinler SA. COVID-19 and thrombosis: from bench to bedside. Trends Cardiovac Med 2020 In Press.

[12] Young E. The anti-inflammatory effects of heparin and related compounds. Thromb Res 2008;122:743–52.

[13] Mummery RS, Rider CC. Characterization of the heparin-binding properties of IL-6. J Immunol 2000;165:5671–9.

[14] de Haan CA, Li Z, te Lintelo E, Bosch BJ, Haijema BJ, Rottier PJ. Murine coronavirus with an extended host range uses heparan sulfate as an entry receptor. J Virol 2005;79:14451–6.

[15] Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A. 2009;106:5871–6.

[16] Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(1):122–4.

[17] White D, MacDonald S, Bull T, Hayman M, de Monteverde-Robb R, Sapsford D, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis 2020;50:287–91.

[18] Choudry FA, Hamshere SM, Rathod KS, Akhtar MM Archbold RA, Guttmann OP, et al. High thrombus burden in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2020;76:1168–76.

[19] Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G, Zeidman A, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. Clin Transl Med 2020;10:e44.

[20] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383:120–8.

[21] Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. N Engl J Med 2020;382:e60.

[22] Bellosta R, Luzzani L, Natalini G, Pegorer MA, Attisani L, Cossu LG, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020;72:1864–72.

[23] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–18.

[24] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020;41:3038–44.