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Review Article

Interrelationship Between Thrombosis and COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus SARS-CoV-2. In March 2020, the World Health Organization officially declared it as pandemic viral infection. Clinical manifestations include fever, dyspnea, cough, but can evolve into acute respiratory distress syndrome (ARDS), and COVID-associated-coagulopathy (CAC). The hypercoagulation state is based on an interaction between thrombosis and inflammation. The so-called CAC represents a key aspect in the genesis of organ damage from SARS-CoV-2. The prothrombotic status in COVID-19 disease cgan be explained by the increase of coagulation, levels of D dimer, lymphocytes, fibrinogen, IL-6 and prothrombin time, that are important laboratory parameters which indicate the COVID-19 and VTE severity.

The main characteristic of immune-thrombosis is the interaction between haemostasis and the innate immune system. The vascular damage in COVID-19 is induced by the endocytosis of SARS-CoV-2 in the host cells, which leads to pyroptosis. This status is a consequence of the direct virus-induced endothelial damage, leukocyte and cytokine-mediated activation of the platelets, release of TF and NETosis, intensified by activation of the complement system. In this review, the aim is providing an overview of the current knowledge on pathogenic mechanisms of thrombosis in different disease states that may occur in COVID-19 and informing on new areas of research.

Keywords: Thrombosis; COVID-19; Hypercoagulation; Inflammatory Cytokine Storm

Abbreviations

VTE: Venous Thromboembolism; COVID-19: Coronavirus Disease 2019; WHO: World Health Organization; ARDS: Acute Respiratory Distress Syndrome; ACE: Angiotensin Converting Enzyme; TNF-α: Tumor Necrosis Factor; IL-6: Interleukine 6; MCP: Monocyte Chemoattractant Protein 1; NK: Natural Killer Cells; TF: Tissue Factor; DAMPs: Damage-Associated Molecular Patterns; PAI-1: Plasminogen Activator Inhibitor 1; TLR: Toll Like Receptor; VWF: Von Willebrand Factor; HIF-1α: Hypoxia Inducible Transcription Factor; INF-γ: Interferon Gamma; MAC: Membrane Attack Complex; NETs: Neutrophil Extracellular Traps; MPO-DNA: Myeloperoxidase DNA; APA: Antiphospholipid Antibodies; aPTT: Activated Partial Thromboplastin Time; LMWH: Low Molecular Weight Heparin; DOAK: Direct Oral Anticoagulants; RTC: Randomized Controlled Trials; VITT: Vaccine-induced Immune Thrombotic Thrombocytopenia

Introduction

The novel coronavirus SARS-CoV-2, that first appeared in the Chinese city of Wuhan, is the virus that causes Coronavirus disease 2019 (COVID-19). It has been declared as a pandemic viral infection by the WORLD Health Organization (WHO) because its spread and the high morbidity and mortality worldwide. By 3 November

2021, COVID-19 had caused 247.472.724 confirmed cases, including 5.012.337 deaths, reported to WHO [1].

SARS-CoV-2 can present with a range of manifestations including fever, coughing, muscle pain, fatigue and can evolve into hyper-inflammation, pneumonia and acute respiratory distress syndrome (ARDS), and COVID-associated-coagulopathy [2]. Hypercoagulable state is strongly associated with coronavirus disease 2019 and may explain several disparate phenomena observed in some critical cases of COVID-19 disease; several mechanism are involved in this process such as inflammatory cytokine storm, platelet activation, endothelial dysfunction and stasis for a long time [3]. In patient who died from COVID-19 the micro thrombosis of alveolar capillary was nine times more prevalent than patient died from influenza and about 15.2% to 79% of patients with severe COVID-19 have shown thrombotic events [4]. Few studies, to date, have analysed the prevalence rate and risk factors of thrombotic complications in COVID-19.

The aim of this review is to provide an overview of the current knowledge on pathogenic mechanisms of thrombosis seen in related disease states that may occur in COVID-19 and potentially inform on new areas of research.

Risk factors

The risk factors for conventional Venous thromboembolism (VTE) are well known, but their use in COVID-19 patients has not yet been validated. The most important intrinsic and extrinsic risk factors for COVID based on the current state of knowledge are summarized in figure 1.

Figure 1: Risk factor of COVID-19.

The mortality linked to COVID-19 is associated with a number of underlying conditions such as increasing age, male sex, obesity, geographic region, multiple chronic comorbidities [5]. In particular, obesity seems to increase the risk of hospitalization and COVID-19 complications [6]. The association between COVID-19 outcomes and overweight/obesity has biological and physiological plausibility. Obesity is emerging as an important risk factor, especially in industrialized countries because it is now known that obese people have twice the risk of serious illness and a 50% higher risk of death [5].

The adipose tissue can serve as a potent inflammatory reservoir for the replication of SARS-Cov - 2 because ACE2 expression levels in adipose tissue is higher than that in lung tissue. People with more adipose tissue, translates into an increased number of ACE2-expressing cells, so that adipose tissue constitutes a reservoir for SARS-CoV-2 increasing the integral viral load [7].

In addition, obese people have low-grade inflammation, which is associated with high leptin levels with pro-inflammatory effects, low adiponectin levels with anti-inflammatory effects and a procoagulant status as well as cytokines and chemokines such as TNF-α, IL-6, and MCP-1 [8]. It has been calculated that one third of total circulating concentrations of IL-6 originate from adipose tissue [9]. The overexpressed pro-inflammatory cytokines in obesity are considered the link between obesity and inflammation.

In addition, obese patients have higher interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) levels in the blood and the natural killer cells (NK) are polarized to non-cytotoxic NK cells. Many authors recommend to classify obese and severely obese patients as high-risk patients for COVID-19 disease. Both obesity and COVID-19 appear to share some common metabolic and inflammatory pathways [6].

Pathogenesis

Since the beginning of the pandemic a very high incidence of thrombo-embolic events (VTE) was observed. The hypercoagulation state, described in patients with COVID-19, caused by a deep and complex inflammatory response to the virus, based on an interaction between thrombosis and inflammation. D-dimer is often altered in hospitalized COVID-19 patients and it has been reported to be a negative prognostic factor associated with high mortality, even if it is not specific [10].

Haemostasis and the immune system complement each other to protect and limit the spread of the virus. Physiological immune-

thrombosis can lead to dysregulation, in that there is an excessive formation of immunologically mediated thrombi and spread, especially in the microcirculation.

In Covid-19 endothelial damage exposes the subendothelial matrix containing tissue factor (TF), their expression on macrophages and platelets could be induced by inflammatory cytokines [11,12].

Immuno-thrombosis appears to be involved in the pathological mechanism of SARS-CoV-2. The prothrombotic status is caused by the immune cell activation, excessive coagulation, and endothelial dysfunction [13]. The main characteristic of immune-thrombosis is the interaction between haemostasis and the innate immune system, especially between monocytes, macrophages and neutrophils. The vascular damage in COVID-19 is induced by the endocytosis of SARS-CoV-2 in the host cells, which leads to pyroptosis.

Pyroptosis is a proinflammatory form of programmed cell death. It ends with cell lysis and the release of various Damage-Associated Molecular Patterns (DAMPs) such as adenosine triphosphate (ATP), nucleic acids and inflammasomes [14]. Pyroptosis releases unencapsulated viral RNA and proteins that infect the surrounding cells and thus intensify the inflammatory environment.

Serological markers

The prothrombotic status in COVID-19 disease can be explained by the increased coagulation, decreased fibrinolysis and immunological effects; serum levels of D - dimer, lymphocytes, fibrinogen, IL-6 and prothrombin time are important laboratory parameters which indicate the COVID-19 and VTE severity.

In fact high D-dimer levels above 1.5 ng/ml (reference values up to 0.5 ng/ml) are a sign of coagulation and fibrinolysis activation and a good indicator for the identification of VTE high-risk populations [15-17].

High levels of D-dimer could indicate a severe inflammatory response associated with a secondary hypercoagulable state: it is also a marker of pulmonary fibrin deposition typical of several lung diseases, commonly seen in severe COVID-19. The D - dimer test can be also used as a highly sensitive test for the detection of active thrombotic processes, but with a low specificity [18].

Moreover IL-6, a marker of hyperinflammatory reaction, can reach high serum levels in patients with severe COVID-19 disease. Many studies have shown an association between increased IL-6 levels and an increased risk of vascular thrombosis and VTE [19]: the combined test of D-dimer and IL-6 offers high sensitivity (up to 96.4%) and specificity (up to 93.3%), allowing an early prediction of the COVID-19 disease severity [20].

Other studies have shown that high IL-6 levels are present in many COVID-19 patients and there is a clear correlation with fibrinogen levels: this supports the theory of inflammatory thrombosis [21].

Moreover, whereas reduced fibrinolysis has been described in patients with COVID-19, the fibrinolytic plasminogen activator inhibitor 1 (PAI-1) is increased in COVID-19 [22].

ACE2 regulation imbalance

SARS-COV-2 infection is mediated by the binding of the viral spike protein to the ACE2 receptor, which is widely expressed not only in the pneumocytes but also in the cardiovascular system cells. The virus penetration into the alveolar epithelium via ACE2 receptor causes the release of inflammatory cytokines such as IL-6, TNF-α etc. and chemokines, which in turn activate epithelial cells, monocytes and neutrophils.

The stimulation of the ACE2 receptor leads to disturbances in the renin-angiotensin system and consequently to vasoconstriction and the release of inflammatory cytokines [23].

The intimate crosstalk between SARS-CoV-2 and ACE2 is not only the interaction between the virus and the receptor, in fact, many pre-existing comorbidities originate from RAS imbalance causing higher risk of infection or a higher risk of mortality after infection [24].

Role of platelets

Platelets play a very important role in the innate immune system by activating the complement and thereby playing a key role in COVID-19 “immune-thrombosis” [25].

PLT activation start when the endothelium is damage interacting with each other or with other cells. The aggregation of PLT increase their potential for pathologic thrombosis; their activation is essential to the development of atherosclerotic plaques and structural remodelling of pulmonary vasculature, linking PLT activation to COPD, inflammation and cardiovascular disease [26,27].

The mechanism of platelet activation may include different and multiple pathways, which appear more complex in the case of Covid-19, where the virus could bind to the cells using several entry mechanisms such as TLRs and/or ACE2-AngII axis [28].

The activated endothelial cells express several proteins such as P-selectin and adhesion molecules, which cause the recruitment of platelets and leukocytes. Activated platelets release several bioactive molecules (e.g. adenosine diphosphate [ADP], polyphosphates, coagulation factors) and immunological mediators (e.g. complement factors), which contributes to activate the immune system through positive feedback [25].

Platelet activation markers such as P-selectin, are increased in patients with COVID-19. P-selectin can lead to a procoagulant phenotype by inducing tissue factor (TF) expression in monocytes. The glycoprotein Von Willebrand factor (VWF) is formed by activated endothelial cells, platelets or the sub endothelial cells and mediates the adhesion and aggregation of platelets. In patients affected by COVID-19, VWF is significantly increased and can indicate a tendency to thrombosis [25,29].

Hypoxia

It has been studied that Hypoxia itself could be a prothrombotic factor in patient with SARS-CoV-2 infection. Hypoxia induces the production of HIF-1α (hypoxia inducible transcription factor) which promotes the endothelial secretion of PAI 1 (plasminogen activator inhibitor) and macrophages. Furthermore hypoxia causes a release of cytokines such as TNF-α and IL-6 [30], critical inflammatory cytokines with protrombotic effects. Positive correlations exisist between IL-6 and D-Dimer, especially during exacerbation of their disease [31].

Vasoconstriction

Endothelial dysfunction is manifested by loss of endothelial cells characteristics like regulating vascular tonus which provokes a prothrombotic status. The down-regulation of the endothelial ACE2 receptor as a consequence of SARS-CoV-2 infection gives a pro-inflammatory, pro-coagulant and pro-apoptotic phenotype to endothelial cells [32].

Cytokines and chemokines

Severe COVID-19 disease is characterized by increased activation of the innate immune system and inflammation which can cause an unrestrained release of cytokine resulting in a phenomenon known as the cytokine storm. This process has been observed in patient with COVID-19 and is related to a more severe disease [33]. Cytokines and chemokines like IL-6, interferon gamma (INF-γ), TNF α, IL-2 and IL-8 are elevated in patients with COVID-19. Pro-inflammatory cytokines such as IL-2, IL-6 and can promote a prothrombotic status: INF-γ and IL-6 have a role in vascular thrombosis increasing platelets production and activity and impairing the endothelium; whereases IL-2 induces the release of plasminogen activator inhibitor (PAI-1), reducing fibrinolysis [34].

Complement

The activation of the complement system is well documented in COVID-19 which is associated with the formation of the terminal membrane attack complex (MAC). MAC can activate platelets with subsequent endothelial damage and secretion of vWF [35].

The activation of the complement leads to an amplification of the prothrombotic phenotype in COVID-19 disease. In fact, C5a can stimulate the release of TF and PAI-1 expression and activate neutrophils, which are responsible for the increased release of IL-6 and IL-8 and the formation of neutrophil extracellular traps (NETs) [36].

Neutrophil extracellular traps

Neutrophils are involved in the early response to pathogens and migrate in site of infection. An important defense mechanism is the so-called NETosis, which is a type of programmed cell death where the nuclei of neutrophils lose their shape and the nucleus breaks down [37]. NETs are structures of DNA, histones and neutrophil antimicrobial proteins that binds and kill pathogens, therefore excessive production of NETs can facilitate microthrombosis by creating a scaffold for platelets aggregation [38]. It has been studied that patients with severe COVID-19 have elevated levels of circulating histones and myeloperoxidase DNA (MPO-DNA) which are two specific markers of NETs [39].

Figure 2: Mechanism of thrombosis in COVID-19.

Additional thrombotic mechanisms

Elevated ferritin levels in COVID-19 reflect cell damage and can contribute to inflammation [40]. High ferritin levels can trigger cell death because of its harmful effects on mitochondria which lead to the release of reactive oxygen radicals [41]. Mitochondrial dysfunction of the platelets can contribute to inflammation and prothrombotic status.

Elevated antiphospholipid antibodies (APA) have been described in COVID-19 [42]. APAs can induce thrombocytopenia and a prolonged activated partial thromboplastin time (aPTT) [43], although their role in inducing COVID-19 associated VTE is currently not entirely clear.

Obesity is associated with a state of prolonged subacute inflammation and is a risk factor for both COVID-19 and VTE [6]. The hypertrophy and the associated dysfunction of the adipocytes causes the release of IL-6, PAI-1 and TF that cause the Activate the coagulation system. The obese people are predisposed to a pro-inflammatory state, through the increase of inflammatory cytokines such as IL-6 and TNF-α. In consideration of this, obese people with COVID-19 disease were more prone to intensive care than others.

In obese people, with the increased production of leptin, which is a pro-inflammatory adipokine, and the decreased production of adiponectin, anti-inflammatory adipokine, platelet aggregation is promoted. This dysregulation could explain the contribution to complications in SARS-CoV-2 patients [8,9].

Therapy and prophylaxis of COVID-19-VTE

A number of substances are used for the therapy of COVID-19-VTE - such as unfractionated heparin, low molecular weight heparin (LMWH), direct oral anticoagulants (DOAK), aggregation inhibitors, factor XII inhibitors, thrombolytic agents, Nafamostat, anti-complement and anti-NET drugs as well as IL-1 receptor antagonist. Several randomized controlled trials (RCTs) are currently underway examining various therapies, combinations and prophylaxis regimens.

Interim results from multiplatform RCTs on VTE prophylaxis show that in moderate COVID-19 disease (hospitalized, not intensive), therapeutic doses of LMWH appear to be better than prophylactic doses - with positive effects on morbidity and mortality and less than 2% severe bleeding [44]. In patients at low or intermediate risk of thrombotic phenomena, treated with prophylactic doses of LMWH has been noticed concomitant reduction of development severe ARDS and venous thromboembolism, that may reduce the need for mechanical ventilation and consequentially the lower cardiovascular death [45].

In severe COVID-19 (intensive care patients), therapeutic doses of heparin did not improve the course, and they seem to be inferior to prophylactic doses. The first strong real-world evidence comes from the USA, from an observational cohort study that examined previous prophylactic anticoagulation versus no anticoagulation in hospitalized COVID-19 patients (not intensive). Immediate treatment with prophylactic heparin was associated with a 34% reduction in relative 30-day mortality risk and an absolute risk reduction of 4.4%. There was no increased risk of bleeding under prophylactic anticoagulation [46].

All guidelines of the medical societies currently recommend VTE prophylaxis, preferably with LMWH, for every inpatient COVID-19 patient. The guidelines do not recommend VTE prophylaxis for COVID-19 outpatients. For inpatients who have been discharged, some guidelines recommend prophylactic anticoagulation for 1-2 weeks if there are additional risk factors [47].

As soon as the data from the RCTs are available, the therapy and prophylaxis recommendations will certainly be adapted and reissued.

Possible mechanism of thrombocytopenia after COVID-19 vaccination

In rare case some patients develop a syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) after COVID-19 vaccination, especially with ChAdOx1 nCoV-19 vaccine. At present, the main hypothesis is that some anti-covid vaccines can promote the synthesis of antibodies against PF4 that provoke platelets' massive activation, inducing immune thrombotic thrombocytopenia [48]. Anti-PF4 antibodies were detected in patients with VITT, in fact current guidelines recommends PF4-heparin ELISA blood test as the first to perform when VITT is clinically suspected [49]. Clot's risk is estimated to be higher in young people (20-29 years old) at 1.1: 100.000, while in general population is around 1:250.000 [50].

Conclusion

COVID-19 is a systemic disease characterized by dysregulation of the immune system and a hypercoagulable status. This status is a consequence of the direct virus-induced endothelial damage, leukocyte and cytokine-mediated activation of the platelets, release of TF and NETosis, intensified by activation of the complement system. The strong activation of the immune system by the SARS-CoV-2 infection leads to a non-regulatable thrombosis, which can present itself with many microthrombi in the micro-vascularization, VTE and arterial events.

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