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REVISION ARTICLE

Pathophysiology of endothelial injury and coagulation alterations in patients with COVID-19

Fisiopatología de la lesión endotelial y las alteraciones de la coagulación en pacientes con COVID-19

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ABSTRACT

Introduction: SARS-CoV-2 infection can frequently induce endothelial injury and coagulation alterations, which has led experts to suggest that the signs and symptoms caused by this virus is comparable to the clinical phenotype of endothelial dysfunction.
Objective: to describe the pathophysiological mechanisms involved in endothelial injury and coagulation alterations in patients with COVID-19.
Methods: a literature review was conducted, using articles retrieved from SciELO, PubMed, EBSCO and Springer.
Development: different pathophysiological mechanisms are associated with endothelial injury and coagulation alterations in patients affected by SARS-CoV-2, either by direct action of the virus on endothelial cells and/or excessive inflammatory response induced by the virus.
Conclusions: the pathophysiological mechanisms involved in endothelial lesion and coagulation alterations in patients with COVID-19 are varied, sharing as a common factor the storm of pro-inflammatory cytokines and conditioning the endothelial lesion itself together with other factors, with the onset of thrombopathies that affects the evolution of the patient.

Keywords: SARS-COV-2; Covid-19; Coronavirus; Endothelial; Blood Coagulation Disorders; Infectious Disease Incubation Period; Communicable Diseases.

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RESUMEN

Introducción: la infección por SARS-CoV-2 puede inducir con frecuencia lesión endotelial y alteraciones de la coagulación, lo que ha llevado a estudiosos del tema a plantear que los signos y síntomas provocados por este virus se asemejan al fenotipo clínico de la disfunción endotelial.
Objetivo: describir los mecanismos fisiopatológicos involucrados en la lesión endotelial y las alteraciones de la coagulación, en pacientes con COVID-19.
Métodos: se realizó una revisión bibliográfica, mediante artículos recuperados en SciELO, PubMed, Ebsco y Springer.
Desarrollo: diferentes mecanismos fisiopatológicos se asocian a la lesión endotelial y las alteraciones de la coagulación en los pacientes afectados por el SARS-CoV-2, ya sea por la acción directa del virus sobre las células endoteliales y/o la excesiva respuesta inflamatoria inducida por el mismo.
Conclusiones: los mecanismos fisiopatológicos involucrados en la lesión endotelial y las alteraciones de la coagulación, en los pacientes con COVID-19, son variados, compartiendo como factor común la tormenta de citoquinas proinflamatorias y condicionando la propia lesión del endotelio unido a otros factores, la aparición de trombopatías que comprometen la evolución del paciente.

Palabras clave: SARS-COV-2; Covid-19; Coronavirus; Endotelial; Coagulopatías; Periodo de Incubación de Enfermedades Infecciosas; Enfermedades Transmisibles.

INTRODUCTION

The first cases of respiratory infection by the new coronavirus were reported in December 2019 in China. Since then, cases multiplied exponentially around the world, causing the collapse of health services in many countries and large numbers of deaths.[1]

On March 11, 2020, the World Health Organization declared a state of pandemic. The virus was named SARS-CoV-2 because of its genetic homology with the severe acute respiratory syndrome coronavirus (SARS-CoV) responsible for a large-scale epidemic in Asia in 2003. The disease was named after the English acronym COVID-19 (Coronavirus Disease identified in 2019).[1]

Coronaviruses are a broad group of viruses enveloped with genetic material such as ribonucleic acid (RNA), between 26 and 32 Kb in length, within the family Coronaviridae. There are 4 genera in the subfamily Orthocoronavirinae, the alphacoronaviruses, betacoronaviruses, gammacoronaviruses and deltacoronaviruses. COVID-19 originates from a new betacoronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has a genome that is a 96 % match to that of a bat coronavirus similar to SARS, indicating a zoonotic origin of the infection.[2]

It is highly contagious and is spread by droplet, direct contact and aerosols. It has been isolated in feces but there is no evidence of transmission by this route. The estimated mean incubation time is 3 to 6 days (range 1.3 to 11.3). Although most patients present mild disease, a percentage develops severe forms of the disease with Acute Respiratory Distress Syndrome (ARDS), mainly associated with older ages and the presence of comorbidities.[1]

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Up to March 9, 2021, 116,736,437 cumulative confirmed cases of COVID-19 were globally reported, including 2,593,285 deaths, of which 45 % of the cases and 48 % of the deaths were added by the Americas region.[3]

In the Americas, between December 2020 and February 2021, the sub-regions of North America (68,9 %) and South America (28,5 %) contributed the largest proportion of cases and for the first time since the first cases were reported, South America contributed a higher proportion of deaths (85 %) of the total, surpassing North America (14,5 %), at the expense of deaths occurring in Brazil.[3]

Up to March 10, 2021, 31 countries and territories in the Americas have reported the presence of variants of concern. Only the United States of America and Canada have reported all three. Some countries/territories have seen an increase in the number of pregnant and postpartum women with COVID-19. A total of 172,552 SARS-CoV-2-positive pregnant women were reported, including 1,017 deaths in the period between the first cases of COVID-19 in the Americas to March 10, 2021.[3]

From May 2020 to March 10, 2021, 3,526 cumulative confirmed cases of Multisystem Inflammatory Syndrome (MIS) in children and adolescents chronologically coincident with COVID-19 were reported, including 95 deaths.[3]

The number of cases and deaths in Healthcare and Care Workers continues to increase, with 1,369,969 cumulative confirmed cases reported, including 7,389 deaths up to March 10, 2021.[3]

In Cuba, to March 11, 59919 cases and 365 deaths had been reported for COVID 19, with a significant increase in the number of cases in the last three months. [4]

METHODS

A literature search was carried out using national and international medical literature, in electronic and printed format in the open access search engine SciELO, PubMed, EBSCO and Springer with the use of the following logical operators: Covid-19; Physiopathology; Endothelial Injury; Coagulopathies.

The search of information sources was conducted between January and May 2021. As a criterion for the selection of the literature, 75 % of the references used corresponded to the last 5 years.

DEVELOPMENT

SARS-CoV-2 contains about 30 000 RNA bases. The set of glycoproteins that envelop the surface of the virus give it the typical *"crown"* appearance. One of them, protein S (spike), is responsible for binding to the cellular receptor ACE-2 (angiotensin-converting enzyme 2) in association with a transmembrane protease known as TMPRSS2, which promotes virus endocytosis.[5]

ACE-2 is a membrane-associated aminopeptidase expressed in different tissues. It was discovered in 2000 as a homologue of angiotensin converting enzyme (ACE). It has been shown to have a potent negative regulatory action on the renin-angiotensin system (RAS), thus contributing to the maintenance of the homeostasis system.[6]

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RAS plays an important role in cardiovascular physiology and homeostasis through the regulation of electrolyte balance, blood pressure and vascular tone.[7] Angiotensin-converting enzyme (ACE) catalyzes the formation of angiotensin II (Ang II) from angiotensin I, playing a key role in the control of cardio-renal function and blood pressure control. Dysfunction of RAS results in elevated Ang II concentrations, which contributes to the increase of oxidative stress, inflammation and, in addition, to the development of metabolic syndrome.[6]

In the RAS, ACE-2 catalyzes the formation of angiotensin (1-7) (Ang 1-7) from Ang II, which allows the reduction of inflammation and oxidative stress stimulated by Ang II, since Ang 1-7 has opposite effects to Ang II, such as vasodilatation, anti-inflammatory effect and anti-proliferative effect.[6]

There are findings that indicate the presence of ACE-2 highly manifested in renal, cardiovascular, gastrointestinal and pulmonary tissues, as well as in oral and nasal mucosa, skin, lymph nodes, thymus, bone marrow, spleen, liver, brain, alveolar epithelial cells type I and II of lung and a remarkable presence, in all the organs studied, in endothelial cells of small and large arterial and venous vessels, as well as in smooth muscle cells of arteries.[6]

SARS-CoV-2 can enter host cells through two mechanisms: *"endosoma binding fusion"* and *"direct binding fusion".* After virus binding, the S1 protein of SARS-CoV -2 binds to ECA 2 in the host cell. Once the virus binds to ACE-2 and internalizes into the cell, this enzyme is functionally disabled preventing the inactivation of Ang II, which could lead to RAS dysfunction, influencing blood pressure and water-electrolyte balance, increasing inflammation and the alteration of vascular permeability in the airways and other systems where receptors for ACE 2 are present.[8]

The binding of the S protein of the virus with the receptors ECA-2 and TMPRSS2 forms a complex that allows the internalization of the virus into the cell, releasing the single-stranded viral RNA genome into the cytoplasm initiating viral replication, which can generate pyroptosis and massive apoptosis of epithelial and endothelial cells, in addition to vascular leakage and pulmonary infiltration of lymphocytes; triggering the release of pro-inflammatory cytokines and chemokines, interleukin (IL)-6 being the main mediator. This phenomenon will stimulate other cells of the immune system to enhance this inflammatory activity, developing a cytokine release syndrome or cytokine storm.[9]

IL-6 is an essential cytokine for maintaining homeostasis in the body, but its excessive production causes chronic inflammation. Virus cleavage in the host endosome stimulates IL-6 protein transcription in host immune cells. This increase in IL-6, together with other factors, induces new signaling pathways that promote the production of IL-6 itself and others in non-immune cells of the organism, generating a positive feedback mechanism, with an overproduction of cytokines.[10]

The cytokine storm begins at a local site of inflammation and then spreads throughout the body through an overproduction of inflammatory cytokines and hemokines released by immune and non-immune cells. This is characterized as a systemic inflammatory response capable of leading to a wide range of clinical manifestations, mediated in numerous cases by endothelial injury and coagulation disturbances, ultimately converging in multi-organ failure.[11, 8]

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Endothelial Injury

The endothelium that lines the interior of blood vessels can be defined as a monolayer that separates the tissues from the blood. Endothelial cells have a multitude of functions including; maintenance of vascular integrity, permeability, cellular and tissue intercommunication, regulation of vasomotor activity, coagulation and inflammation, with specificities that depend on their location. Endothelial dysfunction comprises a loss of balance between endothelium-derived vasodilator and vasoconstrictor factors, where the vasoconstrictor state becomes dominant, leading to progressive pathophysiological changes. Collectively, these endothelial changes exhibit pro-inflammatory, pro-oxidant, proliferative, pro-coagulant, and vascular adhesion characteristics.[12,13]

There are several mechanisms that can cause endothelial injury: free radical injury and proteolytic enzymes. TNF-α increases the toxic action of polymorphonuclear leukocytes; cytokines such as IL-6 and TNF-α induce apoptosis in endothelial cells; direct endothelial injury by CD8+ lymphocytes and natural killer (NK) cells and the mechanism of ischemia whose impact decreases the ATP levels of endothelial cells and induces apoptosis.[14]

Recent evidence suggests that the signs and symptoms of SARS-CoV-2 infection resemble the clinical phenotype of endothelial dysfunction and share mutual pathophysiological mechanisms. Importantly, endothelial dysfunction has been suggested as a major pathophysiologic process in several viral infections, including previous coronaviruses.[15]

Lung aggression by SARS-CoV-2 causes epithelial and endothelial cell disruption, along with alveolar cell inflammation with a high infiltrate of pro-inflammatory cytokines (IL-1, IL-6 and TNF). In severely-ill COVID-19 patients, this immune response is excessive and is therefore described as a systemic "cytokine storm" precipitating the onset of systemic inflammatory response syndrome (SIRS).[16] As described above this cytokine infiltrate can induce apoptosis in endothelial cells.

The glycocalyx that lines the luminal surface of endothelial cells within arteries, veins and micro-vessels has important functions, including maintenance of vascular integrity, permeability, shear, stress, mechanic-sensory and inflammatory functions. Leukocytes passing through a small caliber capillary actually crush the glycocalyx; this transient deformation is quickly corrected due to the elasticity of core proteins that behave like elastic fibers under normal conditions.[13]

In inflammatory conditions such as that caused by cytosine-mediated SARS-CoV-2, protease activation partially degrades the glycocalyx layer, allowing leukocyte rolling, clamping and recruitment, thus losing its ability to regulate the degree of leukocyte capture, recruitment and extravasation.[13]

It is important to note that apoptosis may not require entry of the virus from the host cell, but rather binding to the cell surface and subsequent pro-inflammatory activity and signaling of the apoptotic pathway. [17] Metabolic abnormalities, oxidative stress, chemokines, cytokines, and other by-products cause endothelial cell injury. While the toxic effects may be direct, through altered epigenetic regulation and resident activations, recruited neutrophils and macrophages also contribute products of the vascular injury itself.

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Recruited neutrophil subsets promote inflammation and further injury by releasing TNF-α, IL-1 and IL-8. Endothelial cells produce macro-vesicles in response to inflammatory conditions, which promote neutrophil binding,[18] falling into a vicious cycle that increases inflammation and endothelial injury.

During periods of cell death and immune activation, histones and nucleosomes induce cytotoxicity by altering the permeability of the cell membrane to calcium ions, activating innate immune cells such as complement, which results in a sterile pro-inflammatory environment.[19] The complement system is part of innate immunity and is one of the oldest defense systems. In mammals this system functions as one of the main defense mechanisms and its essential mission is the elimination of pathogens. It is also a double-edged sword, since its absence can lead to a significant susceptibility to infections, but its excessive activation can also be harmful.

In coronavirus infection previous studies have established activation of the complement component C3. In severe forms of COVID-19, other complement activation products (C5b-9, C4d) have been detected, enhancing complement action, which induces endothelial cell injury, platelet and leukocyte activation and the onset of thrombosis in the microcirculation.[20]

Cases of vasculitis are reported especially in children with SARS-CoV-2, ranging from a lymphocytic vasculitis presenting with skin lesions, to a systemic vasculitis similar to Kawasaki disease (KD) caused by an excess of innate immunity in response to virus pathogens. Coronavirus upon binding to ACE 2 increases activation of gene pathways, with immune hyper-responses, decreased lymphocytes, increased monocyte populations secreting cytotoxic cytokines, and increased B and T cell responses, with a deleterious effect on endothelial cells.[21]

Hypoxia caused by severe forms of COVID-19 generates endothelial alterations and a state of hypercoagulability, inducing vasoconstriction with decreased blood supply, with consequent endothelial dysfunction, also causing a shift from the anticoagulant and pro-inflammatory phenotype of the endothelium to a pro-coagulant and pro-inflammatory phenotype.[22]

Recent evidence suggests that severe forms of this disease show a pathophysiology similar to that of complement-mediated thrombotic microangiopathy which is an important regulator of endothelial injury symptoms in this disease.[23]

Pericytes with high expression of receptors for ACE 2 are target cells of COVID-19, resulting in microvascular and endothelial cell dysfunction. Since this type of receptor is expressed in cardiac myocytes, podocytes, tubular epithelial cells of the kidney and in the vasculature of the brain, the occurrence of cardiac, renal and central nervous system injury using this pathway is justified and it has even been proposed that endothelial injury and rupture of cerebral capillaries occurs before neuronal damage.[24]

The vascular endothelial lesions themselves determine a favorable environment for the onset of coagulopathies. Since the modulation of coagulation is a fundamental function of the endothelium, which presents a clear anticoagulant propensity, the purpose of which is to maintain microvascular flow, which is modified when activated by any type of lesion or damage, acquiring a potent pro-coagulant action.

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Coagulation Alterations

Four types of events related to coagulation and thrombus formations are described in COVID-19: cytokine storm and pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-6 stimulate tissue factor expression in immune cells, initiating activation of the extrinsic coagulation pathway; support of the fibrinolytic system by increased release of plasminogen activator or inhibitor 1; platelet activation by various pro-inflammatory cytokines, to damaged endothelium readily binds activated platelets; and direct inflammation-induced endothelial damage.[25]

IL6 plays an important role in the inflammatory mediator network and can cause coagulation disorders through several pathways, such as hepatic stimulation of thrombopoietin and fibrinogen synthesis, increased expression of vascular endothelial growth factor, expression of monocyte tissue factors, and activation of the extrinsic coagulation system. The generated thrombin in turn may induce the vascular endothelium to produce more IL-6 and other cytokines. Cytokine storms and coagulation disorders as a result feedback on each other.[25]

Endothelial cells once activated by endotoxins and/or cytokines, released in response to infection, amplify the inflammatory response, cell movement (polymorphonuclear, macrophages) and expression of protease receptors, which are activated by factor VIIIa, IXa and thrombin. Once activated, they induce the synthesis in endothelial cells of cytokines, chemokines and adhesion molecules.[26]

Associated with this process, endothelial cells lose thrombomodulin and heparin sulfate. There is an increase in the synthesis of tissue factor (TF), which prevents the activation of protein C, tissue factor inhibitor and antithrombin III (ATIII), which associated with the activation of the extrinsic pathway by the expression of tissue factor, modifies the procoagulant/anticoagulant balance with clear procoagulant predominance.[26]

This pathophysiological response significantly modifies the microcirculation. Endothelial cells once activated amplify the inflammatory response, and a vicious circle of inflammation, apoptosis, protein C consumption, activation, dysfunction and endothelial injury is initiated, which evolves into microvascular thrombosis and multiple organ failure.

Antithrombin levels are lower in cases of COVID-19, and D-dimer and fibrinogen levels are higher than in the general population. Progression to disease severity is linked to a gradual increase in D-dimer. These findings support the theory of the development of consumption coagulopathy in SARS-CoV-2 infections, which worsens the prognosis.[27]

Another blood component related to COVID-19 coagulopathies are platelets, which can bind to the virus, either through direct interactions or indirectly through plasma protein bridges, and their binding to the pathogen can trigger their activation and release of burden from their granules. This can play an important role in virus elimination, but in turn conditions platelet aggregation and the onset of thrombosis.[13] When the endothelium is injured, von Willebrand factor exposure increases, which facilitates platelet adhesion and aggregation.

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Alteration of platelets can occur by several routes: indirect damage through invasion of hematopoietic stem cells in the bone marrow or direct damage through complement activation. The inflammation produced in the lung together with hypoxia in cases with pneumonia causes platelet aggregation and thrombosis, with increased platelet consumption. All these factors contribute to trigger the hypercoagulability state seen in COVID-19 cases.[13]

Alterations in fibrinolysis have also been reported in SARS-CoV-2 patients.[28] The regulation of the fibrinolysis system is mediated by specific molecular interactions between its main components and by the synthesis and subsequent release from endothelial cells of plasminogen activators and inhibitors. Therefore, an increase in the activity of the fibrinolysis system favors the occurrence of bleeding disorders, whereas a defect in fibrinolytic activity may predispose to thrombosis.

The most important function of the fibrinolytic system is to degrade fibrin deposits, through the conversion of plasminogen to plasmin, a process catalyzed by activating and inhibitory enzymes of this process, such as tissue plasminogen activator inhibitors (PAI), PAI-1 and PAI-2, which prevent the conversion of plasminogen to plasmin and thus fibrinolysis.[29]

There is a hypercoagulability state in the lungs of patients with ARDS due to COVID-19, leading to fibrin deposition in the intra-alveolar space, which is combined with a hypo-fibrinolytic state, given by an increase primarily PAI-1, although elevated levels of thrombin-activatable fibrinolysis inhibitor (TAFI) and protein C inhibitor are also reported in bronchoalveolar fluid. Platelets have been shown to promote local release of PAI-1, as a significant amount of the active PAI-1 remains associated with the stimulated platelet membrane.[28]

Attenuation of the plasminogen activation system leads to abnormal fibrin turnover in the alveolar space with the occurrence of thrombosis. Plasma levels of PAI-1 have been reported to be a risk factor for poor prognosis and mortality in patients with SARS-CoV-2.[28]

The frequency, with which vascular damage and coagulation disorders occur in severely-ill patients with COVID 19, means that treatment protocols in the world and in Cuba are constantly being improved to prevent and avoid them whenever possible, or to identify them and treat them in a timely approach, avoiding a fatal outcome.

CONCLUSIONS

Multiple pathophysiological mechanisms are involved in endothelial injury and coagulation alterations in patients with COVID-19, including; ischemia, metabolic abnormalities and oxidative stress caused by SARS-CoV-2, the release of cytokines such as IL-6 and TNF-α and other by-products derived by the excessive inflammatory response that cause endothelial cell injury, which, together with other factors such as, the expression of tissue factor in immune cells, induced by the storm of pro-inflammatory cytokines, supported by the fibrinolytic system and platelet activation by various pathways, lead to the onset of thrombopathies that compromise the recovery of the patients.

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Conflict of interest
The authors declare that there is no conflict of interest.

Authors' contribution
MLG: was responsible for conceptualization, formal analysis, project management, writing - original draft, writing - revision and editing.
YHR and RAVP: responsible for conceptualization, formal analysis, project management, writing - original draft, writing - review and editing.
All authors agreed the final manuscript.

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