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.

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EDITORIAL

COVID-19 and cardiovascular disease

COVID-19 y enfermedad cardiovascular

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), also known as COVID-19, has already led to at least one million deaths worldwide, has affected over 40 million people worldwide and a million in Spain.[1] Its fearful impact must therefore not be underestimated. The actual name of the virus is a direct statement of its clinical expression of severely affecting the respiratory system. If to this we add that its transmission is respiratory, it is hardly surprising that the focus of attention has been aimed, in addition to the virological and epidemiological studies, at the expression of the disease in the respiratory system. However, COVID-19 transcends the respiratory system by far, affecting the whole body and also notably, the cardiovascular system. In this sense, the initial focus of attention aims precisely at the virus entry target in the organism, closely linked to the cardiovascular system. SARS-CoV2 presents in the host cells after the binding of the viral spike protein (protein S) to the angiotensin-converting enzyme 2 (ACE2) after its activation by the transmembrane serine protease 2 (TMPRSS2).[2,3] The extensive therapeutic use of the ACE inhibitors (ACEIs) from the beginning led to a broad debate on their effect on the risk of infection by SARS-CoV2. Evidence from extensive epidemiological studies and the preliminary results of an initial randomised clinically controlled trial suggested that the use of ACEIs or angiotensin-II receptor antagonists (AIIRA) do not have a relevant effect per se on the risk of infection or associated complications with COVID-19.[4,5]

The ACE2 are expressed in the epithelial cells of the upper airway and in the type 2 alveolar cells, facilitating transmission of the virus via through the airways. In addition to this, the ACE2 are expressed in the digestive tract, liver, kidneys, central nervous system and brain, and in endothelial cells which provide a substratum for multiorgan involvement, including the cardiovascular system.[6] Thus, the initial image of the syndrome as having respiratory symptoms, acute pulmonary impairment, severe respiratory failure and death is being replaced by that of an exuberant inflammatory response, endothelial inflammation, microvascular thrombosis, disseminated vascular lesions and multiorgan failure.[7,8]

Beyond the cell entry mechanisms for coronavirus, the renin-angiotensis-aldosterone system (RAAS1) may play an essential physiopathological role in cell damage. Angiotensin II is the leading effector cell of RAAS: through the AT1 it causes vasoconstrictive, inflammatory and fibrosing actions,[6] many of which are linked through activation of the nuclear factor kappa B, which also plays a relevant part in 'low-grade' inflammation characterizing arteriosclerosis.[9] Under physiological conditions, ACE2 entails the hydrolysis of the angiotensin II producing angiotensin 1-7 which has anti-inflammatory and antifibrosing properties.[6] Recent results indicate that SARS-CoV-2

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promotes the sweeping of ACE2 from the cell surface through the action of metalloprotease ADAM17 with the subsequent loss of the potential protective ACE2 role in endothelial cells and other organs.[6,10]

Viral diseases, including coronavirus (SARSCoV- 1, SARS-CoV-2 and MERS-CoV), prompt a profound systemic inflammatory response through TLR-3 receptors (Toll-like receptors).[11] TLR-3 are located on the surface area of alveolar cells and bronchial epithelial and other cells of the immune system. TLR-3 recognises the double-stranded DNA of different viral, bacterial or fungal pathogens, following which the dimerization of the receptor occurs, recruiting Toll/IL-1 receptor domain, which in turn contains an adaptor that induces a signalling cascade of interferon-b (TRIF). The cellular immune response involves the activation and proliferation of lymphocytes and macrophages, in addition to raised levels of multiple pro-inflammatory cytokines.[11]

Histological studies show that COVID-19, unlike other viral 'respiratory' infections such as flu, present with a marked vascular involvement with endothelial activation, microangiopathy and thrombosis.[7] It has therefore been suggested that COVID-19 is, above all, an 'endothelial disease'.[8] The vascular endothelium plays a highly relevant role in immune regulation and inflammation in COVID-19. The pro-inflammatory activation of the endothelium generates inflammatory cell recruitment, increased vascular permeability and the development of a prothrombotic state.[12] The accumulation of neutrophil extracellular traps (a process called NETosis) also promotes the development of thrombosis.[13] Under normal conditions, the local inflammatory response helps to control the infection and is self-limiting, recovering the previous situation to the pro-inflammatory insult. However, in a limited number of patients the response is not self-contained and a spike, frequently called a 'cytokine storménsues. This leads to endothelial damage, coagulopathy, and structural organ damage. One extreme (fortunately infrequent) example of this is the development of a syndrome similar to the ''Kawasaki disease in children.[14]

Under physiological conditions, the endothelium is a key element in the balance between pro-coagulating and fibrinolysis, forming a barrier between subendothelial procoagulant and circulatory factors. Under stress, the balance may fall in favour of thrombosis through increased tissue factor expression, the plasminogen activator inhibitor -1 (PAI-1) and the release of the von Willebrand factor. Activation of the coagulation system is a key element in severe COVID-19, as attested by the extraordinary predictive value of severity and death associated with a marked raising of D-dimers.[15–17]

There are many mechanisms leading to heart damage. Firstly, stress and haemodynamic changes may trigger cardiovascular complications, particularly in patients with underlying heart disease. In addition to this, a high prevalence of vascular involvement and myocardial inflammation has been mentioned without the involvement of the large coronary arteries, suggesting that endothelial dysfunction and microvascular thrombosis mechanisms could be more relevant in some patients.[18] In any case, it is interesting to emphasize that the presence of cardiovascular disease (or cardiovascular risk factors such as hypertension and obesity) have a higher prognostic value than a history of chronic obstructive pulmonary disease or asthma in a primarily 'respiratory' disorder.[17,19]

With regard to vascular involvement of other areas, greater incidence of stroke has been described in COVID-19 patients, occasionally in young individuals without any clear vascular risk factors, initially attributable to the prothrombotic disease status.[20] Greater severity of peripheral arterial ischaemia in the context of the COVID -19 pandemic has also been reported.[21] To this increased rate of thrombotic phenomena must be added the risk of the delayed care for acute vascular events due to the reluctance of many patients to attend hospital services and to the saturation of these services.[22,23]

The higher rate of venous thromboembolic disease in the COVID-19 context comes as no surprise, given the beforementioned pro-thrombotic changes, to which must be added the mobility restrictions associated with acute disease and confinements. A prevalence (> 20%) of deep vein thrombosis or pulmonary thromboembolism has been described in patients hospitalised by COVID-19, with an increase in the rate of the most severely ill patients.[16,24] It is of notable interest that anti-thrombotic treatment and /or prophylaxis (particularly with low molecular weight heparin) has been associated with a reduction in mortality in observational studies.[25] It is a matter of debate whether in high risk patients (such as those with a marked elevation of D-dimer) should receive an anti-thrombotic treatment that exceeds the regular prophylactic dose or should include antiplatelets.[26]

Another factor of interest is whether some of the treatments we regularly use in the context of cardiovascular prevention may play a role in the coronavirus disease. As commented above, there is neutrality in the COVID-19 context of treatments with ACEIs and AIIRA,[4] and controversy on the intensity of different anti-thrombotic treatment options.[26] However, retrospective observational studies have reported lower mortality in patients hospitalized with COVID-19 who received treatments with statins.[27] Although statins are of interest due to their potential anti-inflammatory effect,[28] there is no existing evidence to justify their use outside currently authorized indications. Several clinical trials are ongoing which are prospectively assessing the usefulness of treatment with statins, in addition to other drugs used in cardiovascular prevention (anti-thrombotics, colchicine...). A call for serenity and sobriety has arisen: we need to resist succumbing to the 'therapeutic storm' as a response to the 'cytokine storm' within the context of the epidemiological crisis we are experiencing. Despite millions of patients worldwide being affected by COVID-19 and the plethora of associated publications, the lack of randomised clinical trials offering treatments which imply a genuine change in relevant clinical variables of the disease is disheartening.[29] There is an urgent need to seek treatments underpinned by a solid scientific base and meanwhile avoid well-intentioned treatments which are not substantiated by quality controlled trials (*primum non nocere*). Let us optimise cardiovascular prevention measures, including prescribed pharmacological treatments, and participate in controlled trials but let us not engage in treatments which fail to be supported by the best scientific evidence.

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