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Editorial

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Cardiovascular Research at COVID-19

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Abstract

Year 2020 is a historic year for society and challenging for science. With the rise of COVID-19 pandemic, several research groups around the world have studied the structure of the causative virus, potential new drugs, drugs candidates for repurposing, vaccines, and methods of management of the main complications caused by the disease. The new coronavirus can cause several organic complications in respiratory, nervous, urinary, hepatobiliary tissues and bloodstream. Among these complications, it is important to highlight the cardiovascular disorders, since patients with heart disease, systemic arterial hypertension, congestive heart failure, metabolic syndrome and diabetes are some of the main risk groups. In a global alert scenario, the social importance of scientists in cardiovascular research is ratified. Therefore, several research groups have sought strategies aiming the early diagnosis of cardiovascular complications in patients with COVID-19. Additionally, different patient management protocols in intensive care have been designed and constantly revised, which could improve life quality of these patients and minimize mortality rates. Therefore, this editorial for the International Journal of Cardiovascular Research aims to reinforce the importance of research in the area, congratulate the scientists for their efforts in these turbulent times and encourage new studies on this topic, suggesting new experimental and clinical paths.

Keywords

Coagulation; Ischemia; Angiotensin-converting enzyme; Endothelium; SARS-CoV-2; Thrombosis; Stroke.

Introduction

Coronavirus disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which, in many patients, can cause severe pneumonia and acute respiratory failure. Studies show that about one third of infected patients may develop some cardiovascular conditions, especially in individuals with pre-existing disease. To protect these individuals, society and government agencies worldwide have been focused on intensifying prevention measures against infection [1]. In addition, multidisciplinary health professionals are dedicated to improving stratification criteria and management of patients with COVID-19, especially those with cardiovascular complications. Aiming to optimize this collective action, the scientific community proposes some relevant study topics.

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The greatest challenge for the scientific community is to describe the pathophysiology of the disease and the mechanisms involved in organ-specific complications. COVID-19 is a heightened inflammatory and prothrombotic state associated with the occurrence of thromboembolic complications and disseminated intravascular coagulation. The main known pathological features of COVID- 19 so far are virus-mediated lesions in multiple organs, mainly the respiratory tract, and immune response activation, with release of pro-inflammatory cytokines and overactivation of platelet aggregation and coagulation cascade, with micro and macrovascular thrombosis. Among the main complications observed, acute cardiac injury, myocarditis, heart failure, cardiogenic shock or dysrhythmias stand out [2].

The knowledge regarding peculiar inflammatory and coagulative responses on SARS-CoV-2 patients can help understand the multiple organ dysfunctions that transcends the respiratory tract damage. Studies show that more severe patients have a lack of beta-interferon response, perhaps due to genetic polymorphisms, reducing lymphocyte-mediated immune response. These phenomena are associated with lymphopenia and leukopenia, concomitant with increase in the neutrophil/lymphocyte ratio, which has been described as a marker of cardiovascular risk and acute coronary syndrome. Moreover, these inflammatory events lead to rapid pulmonary fibrosis [3].

Additionally, some evidences show that the massive death of pneumocytes after the infection lead to release of inflammatory interleukins, such as IL-1 and IL-6. Consequently, platelets are activated, and small thrombi are formed, bring to microinfarctions, acute coronary syndrome, deep venous thrombosis and even stroke, especially in elderly patients. The pro-thrombotic characteristics of COVID-19 alter homeostasis, increasing risk of ischemic and thromboembolic events. At the heart, this panorama is worrying, as ischemia affects oxidative stress and overload in electron transport chain in mitochondria, which can result in deficit of ATP production and consequent catastrophic death of cardiomyocytes [4].

In this matter, there is a clear association between coagulation and death rates, since a greater incidence of disseminated intravascular coagulation associated with higher levels of D-dimer, greater prolongation of prothrombin time and lower values of fibrinogen and platelets are observed in more severe patients. These pathophysiological mechanisms should be further investigated and may be relevant for the management of these patients. There are several gaps in the literature regarding strategies for preservation of cardiovascular integrity in critical COVID-19 patients. Some subjects are considered important when it is intended to encourage new research, such as circulatory support with oxygenation by extracorporeal membrane, prescription of personalized hemodynamic strategy, as well heparin and other drugs designed to control systemic blood pressure and prevent coronary ischemia [5].

An important discussion involves the use of drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (BRA), thiazolidinediones and ibuprofen, resulting in elevated levels of ACE2 isoenzyme. Although ACE and ACE2 are two structurally related enzymes, ACE2 converts angiotensin II into

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angiotensin (1-7), a peptide hormone with vasodilating and anti-proliferative properties, antagonistic to angiotensin II. Angiotensin II receptor is known to activate metalloprotease 17 (ADAM17), which clivates ACE2 from the cell membrane, thereby increasing soluble ACE2 levels. The recognition and binding of SARS-CoV-2 surface proteins (named spike proteins) to transmembrane ACE2 activate a transmembrane serine protease, TMPRSS2, and promotes the entry of the virus into cells [6].

This is a delicate topic and deserves attention from cardiovascular research scientists. It is known that ACE2 acts in the recovery of ventricular function in patients with myocardial injury. In addition, ACE inhibition prevents angiotensin II production, inhibiting ADAM17 activation and making ACE2 transmembrane available for viral infection. However, some studies have suggested that ACE inhibitors can promote the TMPRSS2-mediated ACE2 cleavage, impairing viral infection [7]. These controversial data indicate that the discontinuity or indication of drugs that interfere with renin-angiotensin-aldosterone system must be further investigated.

Besides that, it is worth mentioning that renin-angiotensin-aldosterone axis is involved on bradykinin metabolism, which has a potent pro-inflammatory action and is part of the lung's innate immune response. Bradykinin cascade is regulated through its degradation by ACE2. Therefore, it was hypothesized that ACE2-spike binding causes bradykinin accumulation in the lung and culminate in exacerbated inflammatory response and pulmonary edema. Furthermore, during acute infection, alveolar ACE2 appears to be under-regulated. This would decrease angiotensin II metabolism, resulting in higher local bradykinin levels, which increases alveolar permeability and promotes lung injury [8].

The inflammatory response and its influence on endothelial function, cardiac muscle and lungs deserves to be highlighted in future methodological approaches; for example, an important point to be analyzed is the relation between the occurrence of myocarditis and acute heart failure in patients with COVID-19. Myocarditis commonly causes major ventricular disorders, associated with diffuse myocardial edema, what would cause electrical disorders related to ventricular dysfunction through myocardial injury, heart failure, Takotsubo syndrome, arrhythmias, and shock. Research in this area should be encouraged, mainly through double-blind, randomized studies, with a relevant sample population and involving individuals of various ages, since most of the studies carried out involve only the elderly [9].

In addition, data related to predictive values, sensitivity, specificity, and robustness of analytical tests are still unclear, specially about biomarkers such as creatine kinase, myoglobin, C-reactive protein, NT-proBNP, troponin, procalcitonin and D-dimer. In addition is important to study the solicitation of transthoracic echocardiography with Doppler and electrocardiogram which, often, indicates the occurrence of ST segment elevation infarctions, with consequent need for catheterization and angioplasty [10].

The scientific community may also focus on manage vascular endothelium and myocardial tissue, especially in microvasculature, as strategies for tissue protection against ischemic and oxidative damage associated to COVID-19. Many patients, even with satisfactory arterial oxygen saturation, develop critical conditions, possibly due to damage of small caliber arterioles and consequent tissue- specific hypoxia. This new scenario is challenging for the scientific community, as COVID-19 is a complex pathology that involves several systemic disorders. Therefore, clinical studies are encouraged, if they are based on well-founded hypotheses and on experimental studies with satisfactory experimental design.

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