ARTÍCULO REVISIÓN

Physical mechanisms involved in cardiovascular damage of COVID-19 carriers

Mecanismos fisiopatogénicos involucrados en el daño cardiovascular en pacientes portadores de la COVID-19

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ABSTRACT

Introduction: COVID-19 is a new disease which provokes damage to human health, with direct impact on the cardiovascular system.
Objective: to describe the pathophysiogenic mechanisms involved in the cardiovascular damage in COVID-19 patients.
Method: a literature review was carried out, through articles retrieved in PubMed, SciELO, EBSCO and ClinicalKey, using 27 references.
Development: different pathophysiogenic mechanisms are associated with cardiovascular damage in COVID-19 patients; among them direct myocardial injury, viral invasion of cardiomyocytes, alteration of myocardial supply-demand index, atheroma-plaque rupture and coronary thrombosis, systemic inflammation and electrolyte imbalances.
Conclusions: determining the mechanisms involved in cardiovascular damage is a fundamental pillar as a preventive and screening strategy in COVID-19 patients. Inflammatory response, secondary hemodynamic changes to the viral process, as well as hypoxemia, are mechanisms of negative impact on cardiovascular health, leading to the development of acute cardiac injury.

Keywords: Cardiovascular Diseases; Coronavirus Infections/Physiopathology

RESUMEN

Introducción: la COVID-19 es una enfermedad nueva con repercusión directa sobre el sistema cardiovascular.
Objetivo: describir los mecanismos fisiopatogénicos involucrados en el daño cardiovascular en pacientes portadores de COVID-19.
Métodos: se realizó una revisión bibliográfica, mediante artículos recuperados en PubMed, SciELO, Ebsco y ClinicalKey. Se emplearon 27 referencias.
Desarrollo: diferentes mecanismos fisiopatológicos se asocian al daño cardiovascular en pacientes con COVID-19, entre ellos la injuria miocárdica directa, invasión viral de los cardiomiocitos, alteración del índice suministro-demanda del miocardio, ruptura de la placa de ateroma y trombosis coronaria, inflamación sistémica, desequilibrios hidroelectrolíticos.
Conclusiones: determinar los mecanismos involucrados en el daño cardiovascular es un pilar fundamental como estrategia preventiva y de tamizaje en estos pacientes. La respuesta inflamatoria, los cambios hemodinámicos secundarios al proceso viral, así como la hipoxemia, constituyen mecanismos de repercusión negativa sobre la salud cardiovascular, llevando al desarrollo de lesión cardiaca aguda.

Palabras clave: Enfermedades Cardiovasculares; Infecciones Por Coronavirus/Fisiopatología.

INTRODUCTION

Coronaviruses (CoVs) are non-segmented positive chain RNA viruses with a genome surrounded by a protein layer. Most CoVs cause disease in their particular host species; those that can infect humans through cross-species transmission have become a major public health threat.[1]

After the SARS-CoV (Severe Acute Respiratory Syndrome- CoronaVirus) of 2003 and the MERS-CoV (Middle East Respiratory Syndrome- CoronaVirus) of 2009, humanity has been attacked again by another coronavirus in 2020, the SARS-CoV-2, and in February of this year the World Health Organization (WHO) named the disease produced by this agent: COVID-19 (coronavirus disease-2019). It was detected for the first time in China, in December 2019, in Wuhan, capital of Hubei province.[2]

This new virus has been reported to spread by air, through Flügge micro-drops emitted from infected people and through contact, whereby it spreads from one person to another or through contact with some contaminated material. More severe patients present symptoms of viral pneumonia including fever, breathing difficulties and bilateral impregnation of the lungs. [1]

SARS-CoV-2 belongs to the subfamily *Orthocoronavirinae*, genus *Coronavirus* and to the subgenus *Sarbecovirus* (beta-coronavirus) and within them to lineage 2. The genome of SARS-CoV-2 consists of a single-stranded RNA of about 30,000 nucleotides and six ORF (open reading frames), identical to the rest of the coronaviruses, and several additional genes. Most of these genes only have 80% homology to the former SARS-CoV virus; however, the genes involved in the replication have 94% homology to this virus.[3] On March 11, 2020, due to the large spread of SARS-CoV-2 around the world, COVID-19 was declared a pandemic.[4]

Since the beginning of the current coronavirus outbreak, there has been great concern about a disease that has rapidly spread in several regions of the world, with different impacts. By March 18, 2020, confirmed positive cases of COVID-19 had already exceeded 214,000 worldwide.(5)

By the end of March, the number of confirmed positive patients exceeded 775,000 in more than 160 countries, and the number of people infected was probably higher. Until then, more than 360,000 people had died from the disease.(6)

According to official data from the WHO, by April 12, 2020, more than 1, 700 000 million cases of COVID-19 had been confirmed worldwide, and deaths exceeded 110,000. In the Americas, the number of confirmed positive cases was 644,986, and more than 25,000 deaths were reported. In Cuba, until that date, 726 cases had been confirmed, of which 21 (2.89 %) died, and 121 (16.6 %) were discharged from the hospital. (7)

In the pathogenesis of SARS-CoV-2 infection it has been suggested the recognition of the angiotensin-converting enzyme 2 (ACE 2) by the S protein of the virus; which is primed by the serin-2 trans-membrane cell protease (TMPRSS 2), facilitating the entry and spread in the receptor cells. ACE 2 is widely expressed in type II pulmonary alveolar cells and capillary endothelial cells. In addition, alveolar cells express TMPRSS2. This explains why COVID-19 is presented as a severe respiratory disease. (8)

Infection of the lung by this virus leads to a cytokine storm with elevated levels of pro-inflammatory cytokines, resulting in edema, air exchange dysfunction, acute respiratory distress and secondary infection, which can result in death. The expression of ACE 2 is also seen in other extra-pulmonary tissues, such as the heart. Such a pattern of expression explains why infected patients in intensive care suffer not only from acute respiratory distress syndrome, but also from other cardiovascular complications.

Although COVID-19 typically presents with symptoms of a lower respiratory tract infection, a significant proportion of patients experience cardiovascular symptoms at the initial presentation of the disease. (9)

Due to the great threat COVID-19 represents at present, together with the existence of a wide dispersion in the scientific literature of contents; the present research is aimed at describing the pathophysiogenic mechanisms involved in cardiovascular damage in COVID-19 patients.

DEVELOPMENT

Among the patients confirmed with SARS-CoV-2 infection by the National Commission of China (NHC), many of the patients demanded medical attention for presenting cardiovascular symptoms such as palpitations and chest pain. Among those who died, 11,8 % of the patients without underlying cardiovascular disease had significant heart damage, with elevated levels of high-sensitivity troponins or cardiac arrest during their hospital stay.(10)

Although the respiratory tract is the primary target for SARS-CoV-2, the cardiovascular system is affected in different ways. There are different pathophysiogenic mechanisms involved in the development of cardiovascular damage in COVID-19 patients.(11)

Direct myocardial injury

SARS-CoV-2 enters human cells by binding to ACE 2, which is highly expressed in the heart and lungs. ACE 2 plays an important role in the neurohumoral regulation of the cardiovascular system in normal health status, as well as in various nosological entities. Fixation of SARS-CoV-2 to ACE 2 may result in alteration of ACE 2 signaling pathways, leading to acute myocardial and pulmonary injury.[12]

Viral invasion of cardiomyocytes

SARS-CoV-2 can invade myocytes and cause direct damage.[13] According to Bansal [14] this is supported by previous autopsy studies in patients who had died of SARS during its outbreak in Toronto. In this study, viral RNA was detected in autopsies in 35 % of the hearts sampled, evidencing direct myocardial injury from the virus.

Alteration of the supply-demand index of myocardium

The increased cardio-metabolic demand associated with systemic infection coupled with hypoxia caused by acute respiratory disease can impair the oxygen supply-demand ratio of the myocardium. This event can lead to acute injury to the myocardium secondary to that hypoxia. [14]

Rupture of atheroma plaque and coronary thrombosis

Systemic inflammation, as well as stress due to increased coronary blood flow, can precipitate the rupture of atheroma plaque. This, together with the alteration of the supply-demand index of myocardium leads to the occurrence of ischemic events, mainly acute myocardial infarction. The prothrombotic environment created by systemic inflammation also increases the risk of infarction.[14]

In a meta-analysis [15] it was reported that, among patients requiring intensive care (20,3 %), 13 % presented ischemic events, and of them 13,9 % died.

In a study in Italy,[16] more than two-thirds of patients who died from COVID-19 had diabetes or a history of ischemic heart disease. Acute myocardial infarction has been recognized as an important factor in the prognosis of viral disease, having suffered a heart attack increases the possibility of developing complications.

Systemic inflammation

The most severe forms of COVID-19 are characterized by acute systemic inflammatory response and cytokine storm, which can result in multiple organ injury leading to multi-organ failure. Studies have shown high circulatory levels of pro-inflammatory cytokines in patients with severe/critical forms of COVID -19 [17,18]

Electrolyte imbalances

Electrolyte imbalances can occur in any critical systemic disease and can precipitate arrhythmias, especially in patients with a history of heart conditions. There is particular interest in hypokalemia in COVID-19, due to the interaction of SARS-CoV-2 with the renin-

angiotensin-aldosterone system. Hypokalemia increases vulnerability for various tachyarrhythmias.[19]

It is difficult to outline the spectrum of cardiovascular presentations of COVID-19. However, based on the available evidence, it appears that cardiovascular sequelae may range from cardiac arrhythmias, acute myocardial injury, myocarditis, and acute coronary syndrome to cardiac collapse and cardiogenic shock.[20]

Several reports [10, 15, 16] have noted the incidence and types of adverse cardiovascular events associated with COVID-19. In one study [21] conducted in China, arrhythmias were present in 16,7 % of hospitalized patients; and 7,2 % experienced acute cardiac injury.

Cardiac injury, defined as a greater than 99th percentile detection of high-sensitivity troponin-I blood levels or the presence of new electrocardiographic or echocardiographic abnormalities, occurred in 19,7 % of patients. These events were more prevalent among older patients and those with associated comorbidities. [21]

According to Ferrari et al., [22] the 26% of the patients hospitalized at Zhongnan University Hospital in Wuhan required intensive cardiovascular care. Out of them, 16.7 % developed arrhythmias and 7,2 % an acute coronary syndrome. According to Fooy et al;[23] the clinical observations suggest cardiovascular complications are an important cause, as well as a significant risk factor of mortality in COVID-19 patients.

Enay et al. [24], in an analysis of 41 COVID-19 patients, the complications included acute respiratory failure (29 %), acute cardiac injury (12 %) and secondary infections (12 %).

Another study [25] published from the retrospective analysis of the database from two hospitals in Wuhan (Jin Yin and Tongii), evaluated 150 confirmed positive cases of SARS-CoV-2, where 68 (48 %) died. Of the patients who died, 63 % presented underlying diseases, with a predominance of cardiovascular diseases. In those patients with associated cardiovascular diseases the risk of death increased.

Palacios-Cruz et al. [26] referred the greatest mortality rate in patients who passed the fifth decade of life, where the presence of comorbidities (cardiac, stroke and diabetes) increased this risk, along with the susceptibility to get ill.

Management of patients with cardiovascular disease and COVID-19

It results important, before the presence of cardiovascular symptoms, to treat the patient as at risk with possible COVID-19 infection, up to rule it out by means of the molecular diagnosis. Several studies have reported [10,15,16,27] the presence of patients in the doctor's offices referring cardiovascular symptoms, without respiratory symptoms, who were subsequently diagnosed with COVID-19.

In the process of COVID-19 management, a rigorous care must be given to both pulmonary and cardiovascular injuries. The early identification, effective and timely treatments, maintenance of the hemodynamic and electrophysiological balance is of great significance in the effective treatment and long-term prognosis of these patients.[27]

The generalities regarding the management of COVID-19 patients, who develop cardiovascular complications or suffer from diagnosed cardiovascular diseases, do not differ from the standard management of a non-COVID-19 patient, according to the guidelines established in the medical practice.[28, 29]

An aspect to consider is to avoid the unnecessary use of diagnostic tests (cardiac troponins and echography); if they are not necessary, likewise the randomization of troponins and natriuretic peptides must be evaded.[27, 29, 30]

Similarly, the medical literature is against discontinuing the therapy with angiotensin-converting enzyme inhibitors (ACEI) and of the angiotensin-receptor antagonists (ARA). [31,32,33]

The Cuban National Health System works taking into account the individualized care of patients, under the precept that there are no diseases, but sick people. The guidelines and information with respect to the management of patients suffering from cardiovascular conditions with COVID-19 or cardiovascular damage secondary to COVID-19 are under constant review and improvement.

CONCLUSIONS

Different pathophysiogenic mechanisms are associated with cardiovascular damage in COVID-19 patients; among them direct myocardial injury, viral invasion of cardiomyocytes, and alteration of myocardial supply-demand index, atheroma-plaque rupture, coronary thrombosis, systemic inflammation along with electrolyte imbalances. The inflammatory response, secondary hemodynamic changes to the viral process, as well as hypoxemia, constitute mechanisms of negative repercussion on the cardiovascular disease, leading to the onset of an acute cardiac injury. The early diagnosis of a cardiovascular disease, based on knowledge in relation to the different pathophysiogenic mechanisms constitutes an essential tool for the prognosis of COVID-19 patients.

Conflict of interests

No conflicts of interests are declared by the authors.

Contribution of authorship

AJPR, SOEG and LCR participated in the conceptualization and design of the article, its writing, revision and approval of its final version.

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