Arrhythmias and their pathophysiological correlations with SARS-COV 2 infection

Arritmias e as suas correlações fisiopatológicas com a infecção do SARS-COV2

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ABSTRACT: Introduction: The pandemic caused by SARS-CoV-2 is considered one of the most critical public health events in the last decades. That said, knowledge of the manifestations of the disease is relevant. Of the changes already described in the literature, cardiac arrhythmias have been receiving increasing prominence. Objective: To discuss the pathogenesis of arrhythmias in the context of the Coronavirus infection and, thus, elucidate the mechanisms of aggression of this virus against cardiac tissue. Methods: This is a cross-sectional and integrative review. Research was carried out in databases such as SciELO, PubMed and Google Scholar. Articles in English, Portuguese and Italian published between 2020 and 2023 were selected. Result: Cardiac arrhythmia because of infection is related to the hyperinflammatory state developed in response to the virus or by direct invasion of structures that have the ACE-2 receptor. Ischemic lesions occur in the sinoatrial node and in the myocardium because of the formation of vascular thrombi caused by inflammation, which impair the rhythm and contraction of this organ, taking it from its sinus rhythm. Regarding direct invasion, the sarcolemma of the cardiomyocytes is ruptured, thus impairing the adequate propagation of the electrical impulse throughout the cardiac tissue and compromises its normal functioning. Conclusion: There is a close relationship between COVID-19 infection and the occurrence of arrhythmias, as well as an increase in morbidity and mortality in infected patients.

KEY WORDS: COVID-19; SARS-CoV-2; Heart; Myocarditis; Coronavirus infections; Arrhythmia.

RESUMO: Introdução: A pandemia causada pelo SARS-CoV-2 é considerada um dos eventos de saúde pública mais críticos das últimas décadas. Posto isso, o conhecimento das manifestações promovidas pela doença se faz relevante. Das alterações já descritas na literatura, as arritmias cardíacas vêm ganhando crescente destaque. Objetivo: Discutir a patogênese das arritmias no contexto da infecção pelo Coronavírus e, assim, elucidar os mecanismos de agressão desse vírus ao tecido cardíaco. Métodos: Trata-se de uma revisão do tipo transversal e integrativa. Pesquisas foram realizadas em bases de dados como SciELO, PubMed e Google Acadêmico. Selecionou-se artigos nos idiomas inglês, português e italiano publicados entre 2020 e 2023. Resultado: A arritmia cardíaca como consequência da infecção possui relação com o estado hiperinflamatório desenvolvido em resposta ao vírus ou pela invasão direta de estruturas que possuam o receptor ECA-2. Ocorrem lesões isquêmicas no nodo sinoatrial e no miocárdio por consequência da formação de trombos vasculares causados pela inflamação, que prejudicam o ritmo e a contração desse órgão, retirando-o de seu ritmo sinusal. No que concerne à invasão direta, há rompimento do sarcolema dos cardiomiócitos, o que prejudica a propagação adequada do impulso elétrico ao longo do tecido cardíaco e compromete seu funcionamento normal. Conclusão: Existe uma estreita relação entre a infecção por COVID-19 e a ocorrência de arritmias, bem como a acentuação da morbimortalidade dos pacientes infectados.

PALAVRAS-CHAVE: COVID-19; SARS-Cov 2; Coração; Miocardite; Infeccões por coronavírus; Arritmia.
INTRODUCTION

From its discovery in the Chinese city Wuhan in December 2019, the affection caused by a Coronavirus family virus scared the world population, due to its quick spread. COVID-19, as named by the World Health Organisation (WHO), is caused by the new coronavirus, so-called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). Due to its fast transmissibility through the upper airways, be it through contact with saliva droplets and secretions present in the air after coughing or sneezing from an infected subject, contact with objects or infected surfaces, or personal contact, the new disease was, then, rapidly declared a pandemic. Because it is a flu-like syndrome, it is possible to list some of its main symptoms: fever, myalgia, headache, dyspepsia, dry cough or wet cough, being dyspepsia and fever the most prominent of them. Most of the symptoms of the patients infected by SARS-CoV-2 do not have high severity, some cases being oligosymptomatic or even completely asymptomatic. Studies suggest that about 20% of the infected people will need admission to hospital and, of those, nearly 25% will require care in an Intensive Care Unit (ICU). Even though the upper airways and, consequently, the lungs are the primarily affected organs, another vital structure is also shown to hold an important role in the infections, considering it is affected in a significant portion of the cases, thus contributing to a worse prognosis: the heart. Analyses of COVID-19 patients in ICU have shown a 36% rate of cardiac damage. More recent studies concerning the pandemic already describe the main damage caused by the new Coronavirus to the cardiovascular system. Among them: myocardial injury, heart failure, Takotsubo syndrome, arrhythmias, myocarditis and shock. The alterations to this system are likely multifactorial and may follow an imbalance between the metabolism demands and the low cardiac reserve, or the systemic hyperinflammatory state and the thrombogenesis. Moreover, there might also be a right myocardial injury caused by the virus itself. Cardiac damage caused by the COVID-19 infection appears as the main factor for cardiac involvement, such as old age, diabetes and systemic arterial hypertension (SAH). Of all the consequences of SARS-CoV-2 infection to the heart, those which stand out are the arrhythmias, since they appear in 16% of the cases. Heart arrhythmias may be defined as a change of the sinus rhythm, that is the physiological heart rhythm that originates on the right atrium and proceeds to the conduction system. Due to its relatively high prevalence, the study of heart arrhythmias in the COVID-19 infection has become essential, since this complication implies an increase of the morbimortality.

For all of that has been said, this study’s main objectives are to analyze the theories and data, and to elucidate the physiopathological mechanisms through which the hyperinflammatory state resulting from the infection is able to provoke myocardial injury.

OBJECTIVE

Review the theories and data concerning the occurrence of heart arrhythmias as a clinical manifestation in patients infected by SARS-CoV-2, emphasizing the pathogenesis of the myocardial injuries resulting from the infectious process and culminating in the organ’s loss of capacity to maintain the sinus rhythm.

METHODS

This is a transversal observational study with the goal of developing an analysis concerning the heart arrhythmias as a clinical manifestation in patients infected by SARS-CoV-2, with focus on the mechanisms involved in the emergence of myocardial injuries as a response to the infectious process.

A search was made through the literature approaching the subject in electronic databases such as Scientific Electronic Library Online (Scielo), PubMed, Google Acadêmico and Publish Or Perish, which allows the study to be classified as an integrative literature review. The terms used for the search were “COVID-19”, “SARS-CoV 2”, “coração” (heart), “miocardite” (myocarditis), “infecções por coronavírus” (coronavirus infection) e “arritmia” (arrhythmia), found in DeCS (Descriptors in Health Sciences). Moreover, there was a preference for recently published articles, from between 2020 and 2023, in order to carry out the analysis based on updated information. After the selection of the material the articles were compared, so that duplicate material was excluded. Afterwards, the articles were entirely read, and those that superficially approached the subject, those that did not approach the physiopathological aspects of the condition, and those with no data on arrhythmias in the infection were excluded. The articles included exposed data we could associate to the coronavirus infection and the arrhythmias - all sorts of rhythm change were considered by the authors -, and also those discussing the hyperinflammatory state cause by the viral antigen studied or mentioning the mechanisms of aggression to the heart tissue that predispose it to arrhythmias, adding up to a total of 19 articles. The articles were later selected and distributed between two authors, who discussed it and rigorously elected the best arguments to be used in this text.

RESULTS

After submitting the compatibility of the collected material approaching the subject chosen for this study and its criteria, a total of 19 articles were gathered. The papers showed a close relationship between the infection by the new Coronavirus and myocardial injury. It was accepted that Systemic Arterial Hypertension (SAH), diabetes and old age are important aggravating factors for this condition. Furthermore, there has been a higher rate of morbimortality in infected patients who had cardiovascular damage. The troponin dosage assists the process of evaluating the patient, having a high Positive Predictive Value (PPV). When it comes to cardiac damage, arrhythmias stood out due to their high incidence, about 16%, and their higher risks to the patients.

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It reveals the clinical importance of the complications resulting from the COVID-19 infection, mostly the respiratory and cardiac ones. Cardiac injury is multifactorial. It may result from an imbalance between metabolic supply and demand and low cardiac reserve or from systemic inflammation. The higher concentrations of cytokines provoked by the hyperinflammatory state caused by the coronavirus infection result in injuries to the cardiovascular system. Cytokines promote more cardiac effort, causing an imbalance between blood supply and demand, which aggravates cell death and rhythm change.

DISCUSSION

Even though this is a subject still full of gaps, as research is being carried out, the damages caused to the cardiovascular system by the new Coronavirus infection have become more and more evident. Among the several manifestations already described in the medical literature and that may appear as a result of the cardiac involvement by the infectious process mentioned, one may list: myocardial injury, Takotsubo Syndrome (TTS), arrhythmias, shock and myocarditis. In this regard, among the comorbidities associated with a higher risk of COVID-19 complications, when it comes to events of cardiac rhythm dysregulation, the presence of heart failure is especially important because it is the outcome of the other pathologies and it leads to death. It is now known that the damage to this system may have multifactorial nature, involving an imbalance between metabolic supply and demand and organ inflammation, or even a direct tissue injury caused by the virus. Even though any subject having been infected by the SARS-CoV-2 presents a potential risk of developing myocardial injury, there should be more concern for those patients carrying risk factors, such as elderly people, people with hypertension and diabetes, knowing for the evaluation of the emergence of arrhythmias after the coronavirus infection, it is recommended to use the echocardiogram and the electrocardiogram. However, such exams may fail to identify mild cases. Conference notes that complications resulting from COVID-19 infection may lead to heart injury. Therefore, all infected patients may be vulnerable to cardiac complications, and arrhythmias among them. The hyperinflammatory state known as “cytokine storm” provoked by SARS-CoV-2 may lead to heart injury. Therefore, all infected patients may be vulnerable to cardiac complications, and arrhythmias among them.

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that these are more susceptible to the development of the severe form of the disease.\textsuperscript{1,22}

From the most different types of manifestations in the cardiovascular system, arrhythmias have been gaining visibility in the last months and have been targeted by new studies in the medical field, once it has a high prevalence among the confirmed cases of COVID-19. According to analysis made in the Chinese city of Wuhan, a considerable portion of the patients have presented arrhythmia events as a consequence of the infection, something that suggests, through quantitative data, the relevance of this complication.\textsuperscript{3}

Studies reveal that the heart injury and the consequent dysregulation of the cardiac rhythm are based on the hyperinflammatory state caused by the infection. The intense stress on the vascular wall associated to the hyperinflammatory state causes the cell death of the organ and the imbalance between the blood supply and demand. Thus, the cardiac muscle tends to enter a state of nutrient occlusion, which predisposes the formation of the thrombi that can partially or completely occlude vases nurturing the conduction system and the cardiac muscle, and, thus, put them in a state of nutrient deprivation and, with consequent cell death and damage by the conduction of the electric impulse and normal contraction, \textsuperscript{3,4}\textsuperscript{.}\textsuperscript{5}

Here, it is understood that the troponin dosage should be used to evaluate the extent of the cardiac damage, because the elevated levels of this marker are a small segment of the total myocardial damage that happens because troponin is the most sensitive cell marker for myocardial injury, detecting even the smaller injuries and, therefore, elevating levels of this protein predict a smaller survival rate.\textsuperscript{6}

In order to explain the relationship between the SARS-CoV-2 infection and the occurrence of cardiac arrhythmias - be them sinus bradycardia or tachycardia, atrioventricular block, or supraventricular or ventricular tachycardia, some hypotheses are convincing and very fundamental, however, it is known that the best way to comprehend this association is the set of physiological mechanisms shedded below.\textsuperscript{7}

Concerning the treatment for the pathology caused by SARS-CoV-2, the use of azithromycin was chosen as an emergency alternative, followed by anticoagulant and antiviral medication and, so far, there have been studies that show the efficacy of this antibiotic is questionable, for its effect was only observed in vitro.\textsuperscript{8,9}\textsuperscript{.}\textsuperscript{10,11}

Moreover, the use of azithromycin has promoted elevation of levels of arrhythmia in patients with COVID-19, a risk factor for heart problems and high death rate, mostly when it is used together with hydroxychloroquine.\textsuperscript{12,13}\textsuperscript{.}

Given the absence of definitive treatment for this condition, the power of vaccination in changing the rates of severe cases of COVID-19 should be measured. Meanwhile, in the prevention of risk factors, as well as raising the people’s awareness to vaccination, are essential measures to decrease cardiac complications and reduce morbi-mortality rates.

**FINAL CONSIDERATIONS**

Through the analysis of the literature, it was possible to infer that heart arrhythmias as a clinical manifestation in patients infected by COVID-19 have a close connection to the hyperinflammatory state and with the “cytokine storm” emerging as a response to the virus. In this context, several injuries to the heart muscle occur due to the inflammatory process in this organ or to the direct invasion of structures having the ACE-2 receptor, which, as a consequence, affect the contraction and the normal rhythm of the heart. Such injuries tend to increase the risk of occurrences, such as elderly people, people with hypertension and diabetes, and thus they should get special attention from the health care teams, so that an adequate management of the complications of the cardiovascular system is made. Despite all of the research carried out so far, understanding of the pathogenic processes involved in these phenomena is not completely solid.