Heart Failure with Preserved Ejection Fraction and COVID-19: a Pernicious Relationship

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Introduction

The ongoing pandemic of Severe Acute Respiratory Virus-2 (SARS-CoV2) infection was first recognized in China in 2019 and brought significant health and economic threats around the world. On January 31, 2020, the World Health Organization (WHO) declared the disease caused by SARS-CoV2 an international public health emergency and on March 11, 2020, the WHO declared it a pandemic.1,2 Three months after the initial WHO declaration, there were more than 5 million confirmed cases worldwide and 300,000 deaths. In Brazil, in the same time interval, there were more than 850,000 cases and 43,000 deaths, with an upward trend.3

The epidemiological and clinical severity of the pandemic by COVID-19 was initially supported by 4 alarming elements: (a) respiratory transmission with a high infectivity rate; (b) high lethality in specific subgroups; (c) high demand for intensive care and mechanical ventilation; and (d) no effective vaccine or specific treatment. Given the magnitude of the problem and the scarcity of resources, there was a recommendation for hospitalizing critically ill patients and providing them with supportive treatment and, above all, mitigation via social isolation aimed at flattening out the epidemic curve.4-12

COVID-19 and cardiovascular diseases

Among the various clinical manifestations of COVID-19, cardiovascular complications are one of the most significant and with a potential risk of mortality. COVID-19 may present with respiratory failure secondary to pneumonia; acute respiratory distress syndrome; and severe cardiac injury characterized by high troponin and heart failure (HF). This presentation is associated with increased mortality.

The COVID-19 pandemic imposes a double burden on people with cardiovascular disease (CVD). About 40% of patients hospitalized with COVID-19 have CVD with a worse clinical outcome. Many of the most severe manifestations, such as myocardial injury, can occur between 8 and 14 days after the onset of symptoms. Several observational studies from Chinese and European series have identified advanced age and the presence of comorbidities, such as diabetes, hypertension, atherosclerotic coronary disease (CAD), and chronic obstructive pulmonary disease (COPD), as predictors of progression to severe illnesses, with higher lethality.

The increase in the frequency of adverse cardiovascular events after the resolution of COVID-19, similar to other viral infections such as influenza, may also play a role in mortality of patients with COVID-19. Thus, understanding the relationship between the immune response of the viral host and the cardiovascular system will be extremely important in the care and treatment of patients with COVID-19.13 Several mechanisms are related to cardiac injury in patients with COVID-19, such as direct viral myocardial injury, microvascular injury, stress cardiomyopathy (Takotsubo), acute coronary syndrome, myocardial injury due to an imbalance in oxygen supply and demand, and systemic inflammatory response with myocardial injury.14 This could be specially deleterious in patients with HF with preserved ejection fraction (HFP EF), in whom baseline diseases such as diabetes and hypertension are prevalent (Figure 1).
COVID-19 and Heart Failure

HF is associated with high morbidity and mortality with high costs for the health system and represents the final phenotype of many cardiovascular disorders. In recent decades, the incidence of HF has remained stable, however the prevalence has increased over time, mainly in relation to HFpEF, probably due to the longer survival of patients secondary to the available therapeutic resources. A study conducted in the population served by the Family Medical Program in Niterói, state of Rio de Janeiro, showed a prevalence of HF of 9.3%, of which 59% had the HFpEF phenotype, assessed in individuals aged 45 years or over.15

In general, patients with HFpEF are older, women, and diagnosed with hypertension. The prevalence of other risk factors varies according to the criteria used in the methodology to define and select patients with HFpEF16,17 (figure 2). Biomarkers with a prognostic impact on CVD can be valuable in this high risk subgroup. Hospitalized patients should have their levels of natriuretic peptides, D-dimer, and troponin monitored. Troponin, in particular, can be an ally in the early detection of cardiac complications.18 Small elevations (2 to 3 times above the cutoff), may be due to pre-existing diseases. However, high elevations (> 5 times above the cutoff) may be the result of severe respiratory failure, tachycardia, hypoxia, or shock, due to COVID-19, or indicate direct myocardial injury as seen in myocarditis, Takotsubo syndrome, or even type 1 acute myocardial infarction, triggered by COVID-19.19 The measurement of these biomarkers in an outpatient setting has not been studied, but it could be useful for monitoring signs of severity in this high risk group, along with O2 saturation.

Metabolic diseases, COVID-19, and HFpEF

In the metabolic context, obesity and dysglycemia are common comorbidities in HFpEF. Obesity determines hemodynamic overload, left ventricular and atrial remodeling, in addition to activation of the renin-angiotensin-aldosterone system, a mechanism directly involved in the pathophysiology of COVID-19. Furthermore, obesity stimulates the sympathetic nervous system, natriuretic peptides, Adiponectin-induced inflammatory diseases and oxidative stress. This altered milieu results in different degrees of myocardial and vascular functional impairment, usually without significant systolic ventricular dysfunction, but with a typical phenotypic manifestation of HFpEF.20

Recent data show that people with obesity may also experience more symptoms of COVID-19 and are more
likely to need intensive treatment. A retrospective cohort study found that patients with severe obesity defined by a body mass index (BMI) >40 kg/m² who contracted COVID-19 in France were more likely to have mechanical ventilation, regardless of the presence of advanced age, hypertension, or diabetes.²⁷,²⁸

The position of the European Association for the Study of Obesity on COVID-19 shows concern about the possibility of weight gain in quarantined patients and recommends caloric control in the diet, as well as good glycemic control in those who are also diabetic, as a method of try to reduce the risk and severity of infection.²¹

Diabetes plays a central role in the interaction of HFpEF and COVID-19. Diabetes is a primary risk factor for the development of severe pneumonia and sepsis due to viral infections in general. In parallel, glycemic dysregulation associated with insulin resistance is associated with progressive changes in cardiac structure and function that result in myocardial remodeling and left ventricular systolic and diastolic dysfunction. More specifically, diabetes can determine diabetic cardiomyopathy, and may be associated with HF manifestations and higher frequency of clinical complications resulting from this syndrome.²² The occurrence of the association of diabetes with structural heart disease typical of HFpEF is, therefore, a first explanation for the increased susceptibility of diabetic patients to complications in COVID-19. Another possibility may be associated with innate defects of immunity, affecting the cellular immune response mediated by viral aggression.²³

When affected by COVID-19, diabetic patients experience exacerbated hyperglycemia, especially in older individuals.²⁴ Acute hyperglycemia has been associated with the activation of the angiotensin-converting enzyme 2 (ACE-2), which is the receptor for the coronavirus spike protein. Coronavirus infection reduces the expression of ACE2, inducing cell damage, hyperinflammation, and respiratory failure.²⁵ In addition, the virus has the potential to damage pancreatic beta cells, which can determine insulin deficiency and frequent cases of severe diabetic ketoacidosis on hospital admission.²³

The COVID-19 event in diabetic patients, therefore, affected even the recommendations for drug treatment of type II diabetes. A group of drugs strongly indicated for the treatment in the context of high cardiovascular risk, frequent in HFpEF, are the Sodium-Glucose-Cotransporter 2 (SGLT2) inhibitors. Initial reports associated these drugs with an increased risk of developing ketosis in insulinopenic patients (type I
diabetes and some type II diabetes). In this scenario, a recent positioning of the Brazilian Societies of Diabetes, Endocrinology and Metabolism, and Cardiology defined safety recommendations for the use of these drugs. In summary, the document does not recommend the use of SGLT2 inhibitors in patients with type I diabetes; suggests suspension in patients with type 2 diabetes, prone or not to ketosis, who are simultaneously using insulin, in case of symptomatic infection by the Coronavirus; does not recommend SGLT2 inhibitors for patients without diabetes or with pre-diabetes to reduce cardiovascular risk, and also does not recommend the use of SGLT2 inhibitors in hospitalized patients due to the increased risk of dehydration. The content of these recommendations is based on the principle of patient safety in the COVID-19 pandemic scenario. Therefore, it does not seem relevant to discuss the potential withdrawal of the benefits of SGLT2 inhibitors to such patients with diabetes and HFpEF in the medium and long term.

**Cardiovascular Disease and Prognosis in COVID-19**

Preliminary data from the COVID-19 case series suggested that hypertension correlates with worse results (23.2%) compared to other metabolic disorders. It was postulated that this observation was correlated with the use of ACE inhibitors or angiotensin receptor blockers (ARB) instead of hypertension itself. This supposed correlation was rapidly disseminated among medical communities, which encouraged the hasty withdrawal of the use of these drugs in patients with COVID-19.

This worsening seems to be related to the endocytosis of SARS-CoV2, which is mediated by the ACE-2 receptor and is fundamental in the viral life cycle. There are conflicting data on the effect of inhibitors of the renin-angiotensin-aldosterone system, including ACE inhibitors and ARB, on ACE2 activity in various human tissues and the resulting susceptibility to SARS-CoV2 infection. All available data are insufficient to recommend discontinuation of ACE inhibitors or ARBs in individuals with an existing indication for therapy with these drugs, and the main medical societies strongly recommended continuation of treatment. An open randomized study is underway to examine the effect of prophylactic withdrawal from ACE inhibitors or ARBs in individuals with COVID-19.

Although the ACE-2 receptor may allow SARS-CoV2 to enter cells, its free circulation forms could then inactivate the virus, interrupting coupling to membrane ACE-2 receptors and the consequent entry into pulmonary endothelial cells. However, the circulating plasma level of ACE-2 may be insufficient to protect the ACE-2 receptors connected to the SARS-CoV2 coupling membrane. In addition to circulating soluble ACE-2, it was observed that mineralocorticoid receptor antagonists such as spironolactone, with a well-studied safety and risk profile, increase the expression of soluble ECA-2 in the plasma by 3 to 5 times.

Three recent studies, with a large number of patients, evaluated the risk of using ACE inhibitors or ARBs in patients with COVID-19. A study that evaluated a potential harmful effect of ACE inhibitors and ARBs in 8910 patients hospitalized with COVID-19 showed that there was no potential harmful association between the use of ACE inhibitors or ARBs with hospital death in this clinical context. Another study that evaluated 6272 patients with severe SARS-CoV-2 infection, where the use of ACE inhibitors and ARBs was more frequent in patients with Covid-19 than in the control group, showed no association between the use of ACE inhibitors or ARBs with a severe or fatal COVID-19 course. Finally, Reynolds HR et al., evaluating in 12 594 patients the relationship between treatment with ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and thiazide diuretics and the potential risk of these drugs in patients with COVID-19 showed that there was no substantial increase in relation to the association of these 5 common classes of antihypertensive drugs with the risk of developing severe conditions in patients who tested positive for COVID-19.

The benefits of spironolactone in patients with HFpEF were assessed in the TOPCAT study, which showed a reduction in the number of hospital admissions for HF. In patients with hypertension, spironolactone is widely used, being indicated as the fourth medication in the treatment of resistant arterial hypertension.

More recently, a hypothesis has suggested that inhibition of the angiotensin 1 receptor (AT1R) may provide benefits to patients with COVID-19. AT1R antagonists are widely used in hypertensive patients and increase the cardiac expression of ACE2 in rats and the urinary concentration of ACE2. Therefore, a higher expression of ACE2 after chronic therapy with angiotensin receptor blockers can protect patients with COVID-19 from acute lung injury. In this scenario, the role of neprilisin (NEP) and its sacubitrile
inhibitor should also be reviewed. Recently, Zhang et al. demonstrated that sacubitril / valsartan reduced the concentration of pro-inflammatory cytokines and the neutrophil count, while increasing the lymphocyte count more than valsartan alone or placebo in patients with acute HF. This evidence supports the biological plausibility of the early administration of sacubitril / valsartan in patients with COVID-19, in order to maximize the anti-inflammatory effects of sacubitril and contain the effect of Angiotensin I in the lungs. It should be noted, however, that there has been no clinical studies evaluating cardiovascular outcomes that support this practice.

**Therapeutics for COVID-19 and Cardiovascular Disease**

HFpEF patients with multiple comorbidities are at high risk of death in the case of SARS-CoV2 infection, therefore it is imperative to take preventive measures. To date, there is no vaccine to prevent COVID-19. The best prevention is to avoid exposure to the virus. The usual preventive measures that can reduce the risk of exposure include: wearing face masks; regular hand washing with soap or disinfection with hand sanitizer containing at least 70% alcohol; avoiding contact with infected people, keeping an adequate distance; and refraining from touching the eyes, nose and mouth with unwashed hands. In addition, patients with HFpEF should be vaccinated against pneumococcal pneumonia and influenza.

Social isolation to prevent COVID-19 does not necessarily mean the adoption of a sedentary lifestyle. Patients with HFpEF in functional class II and III benefit from regular aerobic exercise to improve their functional capacity and diastolic function. Whenever possible and within the precautions of respiratory contamination, exercise should be maintained.

HFpEF patients use polypharmacy to control comorbidities such as angiotensin-converting enzyme (ACEI) inhibitors, diuretics, statins, oral hypoglycemic agents, and some medications that can reduce hospitalization due to HF decompensation, such as spironolactone, candesartan, nebivolol and sacubitril / valsartan, in female patients and with a left ventricular ejection fraction of less than 57%, as evidenced in the PARAGON-HF Study. Such prior medications must be maintained in the pandemic and in the eventual contamination by the virus.

The antiviral properties of chloroquine (CQ) were previously observed in HIV and other viruses. It has been postulated that CQ and Hydroxychloroquine (HCQ) inhibit endosomal maturation, a process by which endosomes are translocated from the cell to central hubs. In addition, CQ could prevent the viral replication of SARS-CoV1 in vitro. A follow-up study demonstrated comparable effectiveness of HCQ, a less toxic derivative, and suggested that the mechanism of decreased endosomal maturation did indeed apply to SARS-CoV2 infection in vitro. So far, the role of HCQ in COVID-19 has only been evaluated in non-blind, non-randomized, and low-quality studies. At the time of writing this article, CQ and HCQ have clinical off-label use authorized by the Federal Council of Medicine. There are ongoing clinical trials which assess the in vivo outcome of this hypothetical property. In addition, CQ and HCQ prolong the QT interval, which increases the risk of a pro-arrhythmic effect. Significant caution should therefore be taken when initiating these agents in patients with a QTc interval >500ms, in those with congenital long QT syndrome, with structural heart disease, or under concomitant use of other QT interval prolonging agents. In fact, a recently published observational study with more than 96,000 patients hospitalized for COVID-19 showed an increased risk of death with HCQ and CQ when used alone or in association with a macrolide.

**Chloroquine and Hydroxychloroquine cardiomyopathy**

There are case reports which relate the use of CQ and HCQ with the onset of diastolic and systolic ventricular dysfunction, dilated cardiomyopathy, pulmonary hypertension secondary to left ventricular dysfunction, atrioventricular blocks, and ventricular tachyarrhythmias. In most cases, reversibility is observed after drug withdrawal. Diagnostic confirmation is given by the presence of cytoplasmic curvilinear bodies on electron microscopy of the cardiac muscle added to the clinical history of using CQ or HCQ, and the absence of other factors. A possible genetic predisposition is speculated such as the polymorphism of α-galactosidase A, the genetic basis of Fabry’s disease. Both CQ / HCQ cardiomyopathy and Fabry disease have clinical and histological similarities.
Pandemic and Delayed Care for Patients with Decompensated HF

The evidence that the hospital can be a place where the infection can be contracted has dramatically reduced the access of non-COVID-19 patients to emergency care and emergency services, as well as elective hospital activities not related to COVID-19. The need to reorganize hospital activities to treat patients who suffer from severe forms of COVID-19 requires us to learn the safe treatment of patients who stay at home with milder forms of COVID-19, and the need to keep more vulnerable individuals, such as those with HFpEF, out of hospital. The flexible use of tools such as telemedicine, for integration and not as an alternative to traditional care, adapted to the needs of clinical, family and social health contexts, could allow the creation of personalized, effective, and efficient management programs for the care of these patients, as recommended in the II Brazilian Directive on Telemedicine in Cardiology of the Brazilian Society of Cardiology.

Final considerations

HFpEF is multifactorial and has a pathophysiological relationship with multiple comorbidities such as hypertension, diabetes, obesity, atrial fibrillation, advanced age, and atherosclerosis. The systemic inflammatory state is a common link between these elements. COVID-19 has a well-defined etiological agent; however, its morbidity and lethality vary with the host. The intense systemic inflammatory response also seems to be the link that explains the worsening of the clinical condition. Comorbidities have emerged as predictors of poor prognosis in SARS-CoV2 infection since the beginning of its description, and in both HFpEF and COVID-19, they constitute the pernicious and disastrous element. If they are in pairs - HFpEF and COVID-19 - maximum alert, double care.

Author contributions

Conception and design of the research: Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA. Writing of the manuscript Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA. Critical revision of the manuscript for intellectual content: Mesquita ET; Jorge AJL; Villacorta Junior H; Danzmann LC; Martins WA.

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References

Viewpoint


