Heart failure and Covid19

A Review Article

A Review Article Submitted in Partial Fulfillment of the Requirements for the Degree of Bachelor in Medicine at University of Diyala

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2021-2022

Table of Contents

Introduction

Coronaviruses are a large family of single positive-stranded, enveloped RNA viruses that can infect many animal species and humans. Human coronaviruses can be divided based on their pathogenicity. The types with high pathogenicity including SARS-CoV, MERS-CoV, and the current novel SARS-CoV2 (1).Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was identified in December 2019 in Wuhan, China, and has evolved into a global health crisis. The full spectrum of SARS-CoV-2 infections in humans is not fully understood yet, but is being heavily studied. Patients with previously established comorbidities such as heart failure (HF) are at a particularly high risk of morbidity and mortality from this viral infection (2).

The clinical features related to this 'new' coronavirus are similar to the ones caused by other coronaviruses known for past epidemics, such as SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, although epidemiological data point at a lower mortality. The clinical characteristics of (COVID-19) have rapidly increased interest and concerns. As described by the first analyses on the Chinese population, a severe clinical evolution of pneumonia, with a sustained risk of intensive care admission, intubation and death represents a recurrent in patients of advanced age or affected by chronic diseases (3).

Heart failure (HF) is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or the ejection of blood. The most common cause for HF is reduced left ventricular myocardial function; however, dysfunction of the pericardium, myocardium, endocardium, heart valves or great vessels alone or in combination is also associated with HF. Some of the major pathogenic mechanisms leading to HF are increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neuro-humoral

stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis and genetic mutations (26).

Heart failure can be classified as predominantly left ventricular, right ventricular or biventricular based on the location of the deficit. Depending on the time of onset, HF is classified as acute or chronic. Clinically, it is typically classified into two major types based on the functional status of heart: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). In patients with HFpEF who are mostly females and older adults, EF is usually more than 50%; the volume of the left-ventricular (LV) cavity is typically normal, but the LV wall is thickened and stiff; hence, the ratio of LV mass/end-diastolic volume is high (27). The clinical presentation of HF comprises symptoms of shortness of breath (SOB)/dyspnea (sensitivity of 84%–100%, but a specificity of 17%–34%); orthopnea/SOB on lying own (sensitivity of 22%–50% and a specificity of 74%–77%); paroxysmal nocturnal dyspnea (sensitivity 39%–41%, specificity from 80%–84%); fatigue/weakness/lethargy (due to HF-induced circulation-related abnormalities in skeletal muscles); edema, abdominal distention and right hypochondrial pain (most likely due to right-sided heart failure with sensitivity and specificity of 23% and 80%, respectively) (28).

The underlying pathogenesis of HF also involves silent inflammatory and immune-regulatory responses, the activation of which still has not been completely understood. It has been proposed that in HF, excessive neuroendocrine activation leads to the activation of neuro-hormones and pro-inflammatory cytokines following an initial cardiac insult. Many of these pro-inflammatory and anti-inflammatory cytokines and their receptors, released endotoxins, adhesion molecules, nitric oxide

and reactive oxygen species have been associated with various pathological aspects of HF (29).

Although COVID-19 was initially considered a respiratory disease, it has rapidly become clear that a multiorgan involvement was common. In particular, the heart often represents a target organ and patients may develop heart failure (HF) (4). Of note, the link between COVID-19 and HF is more complex. First, COVID-19 pandemic has an impact on HF management and a reduction of hospitalizations due to HF has been shown during the pandemic period, possibly leading to an increase in HF mortality. Second, history of HF is a risk factor for a more severe clinical course of COVID-19. Third, HF can be a consequence of COVID-19-related myocardial damage (5).

In this review, we will discuss the relation between COVID-19 and Heart failure and the impact of the infection on chronic patients.

Review of literature

Patients with a history of cardiovascular (CV) disease, heart failure (HF), and/or CV risk factors seem to be at higher risk for COVID-19 and an unfavourable clinical course once infected. A possible explanation might be the pre-existing endothelial dysfunction. Various cardiac manifestations during COVID-19 have been reported, and biomarkers of cardiac damage are increased in 5–25% of hospitalized COVID-19 patients. Studies have demonstrated an increased mortality in patients with concomitant CV disease (6). A large retrospective cohort study in US veterans tested positive for SARS-CoV-2 in the ambulatory setting reported that patients with COVID-19 and previously diagnosed HF had a higher risk of hospital admissions and 30 day mortality (7). An impaired prognosis can be expected in patients requiring hospitalization with COVID-19 diagnosis. Single-centre and

nationwide cohort studies showed that COVID-19 affected referral and hospitalizations of patients with acute HF and that HF was associated with high mortality (8).

Cardiovascular disease and CV risk factors have been increasingly recognized as predisposing determinants of worse outcomes in COVID-19 since the beginning of the pandemic. However, the role of HF remains elusive. In multinational multi center registry, it showed a higher mortality for hospitalized COVID-19 patients with HF compared with patients without HF, even after adjustment for other conditions and co-morbidities. Particularly, patients experiencing an HF event during hospitalization for COVID-19 are at high risk for death, an important proportion of whom did not have a history of HF. The cause of death in most cases was not related to respiratory failure alone but rather to multi-organ failure (9).

Pre-existing HF or risk factors for HF will predispose subjects to HF as a complication of any viral infection. More specifically, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2), expressed by epithelial cells of the lung, as the receptor-binding domain for its spike protein to gain entry to the epithelium. ACE2 (and ACE) gene expression is up-regulated in HF. This could theoretically increase susceptibility to infection (10). It has also been speculated that drugs widely used for hypertension, diabetes and HF – such as ACE inhibitors and angiotensin receptor blockers (ARB) – can lead to upregulation of ACE2 (including at the cardiac level which could in theory increase susceptibility to the infection. However, at present, there is no evidence for this, and there have been very clear statements from the American College of Cardiology, American Heart Association, Heart Failure Society of America and the British Cardiovascular Society that these drugs should not be discontinued (11). Whilst up-regulation of ACE2 could lead to increased susceptibility to infection, it might have a protective effect

on the injury caused by the virus. Binding of SARS-CoV-2 to ACE2 results in down-regulation of ACE2, leading to greater production of angiotensin II (which may already be high in patients with HF), since the function of ACE2 is a negative regulator of the renin–angiotensin–aldosterone system (RAAS) through the inactivation of angiotensin II to angiotensin (1–7), a potent vasodilator acting through the Mas receptor (12).

The prevalence of HF in the population susceptible to COVID-19 is significant and so is the prevalence of predisposing conditions which put infected patients at risk of developing HF. In a multicenter retrospective study from New York City area, including nearly 3,000 patients with laboratory-confirmed SARS-CoV-2 infection, the prevalence of HF was 10.1%. HF patients were more prone to develop myocardial injury, defined as increased troponin levels. HF history was also found to be associated with an increased risk of hospitalization and a severe clinical course in COVID-19 patients (13). In another prospective cohort study, among 5,279 people with laboratory confirmed SARS-CoV-2 infection, more than a half were admitted to hospital, of whom 1,904 (69.5%) were discharged alive. Besides age, HF was one of the strongest predictor for in-hospital admission and critical illness (14). A retrospective analysis conducted in Spain showed that HF was associated with higher risk of mechanical ventilation and mortality among patients hospitalized for COVID-19, regardless of left ventricle ejection fraction (LVEF) (6).

COVID-19 has general deleterious effects on the cardiovascular system, which were already described in other infections (i.e., influenza and community-acquired pneumoniae). Fever and sympathetic activation cause tachycardia with a consequent increase in myocardial oxygen consumption. Moreover, prolonged bed rest and systemic inflammation favor coagulation disorders. Both venous and unusual arterial thromboembolic events were observed in COVID-19 patients. Hypoxemia,

another hallmark of COVID-19, is associated with enhanced oxidative stress with reactive oxygen species production and subsequent intracellular acidosis, mitochondrial damage, and cell death (15).

A series of indirect mechanisms are those related with the peculiar abnormal inflammatory response that COVID-19 may elicit: the presence of a proinflammatory surge, the so-called cytokine storm, may happen in a week after the infection and is thought to be central in the pathogenesis of the acute lung injury/ARDS spectrum, as it is reported in severely ill patients (16). In addition, the hyperinflammation syndrome seems to be pivotal in the development of cardiac injury, since a positive correlation has been described between the increase in inflammatory markers and myocardial damage in COVID-19 (17). Consistently, previous *in-vitro* studies have shown that the release of proinflammatory cytokines such as TNF and IL-1β, in other septic conditions, were responsible for myocardial cells depression, through modulation of calcium channel activity and nitric oxide production (18). Cytokine storm may be as well the cause of acute HF: the inflammatory activation and oxidative stress are similarly present in HF and may predispose, combined with COVID-19, to a more severe clinical course. Finally, the marked inflammatory response takes place also in the endothelium, as demonstrated by post-mortem histological findings showing lymphocytic endotheliitis with apoptotic bodies and viral inclusion structures in multiple organs. Endotheliitis can lead to disseminated intravascular coagulation with small or large vessels thrombosis and infarction and significant new vessel growth through a mechanism of intussusceptive angiogenesis (19).

Patients hospitalized for HF during the pandemic were sicker, with higher rates of NYHA class III or IV symptoms and severe peripheral edema, which are known predictors of poor outcomes in acute HF. The authors speculated that patients with

less severe acute HF might have avoided presenting to hospital during the pandemic, due to the fear of acquiring infection (20). Further studies aimed to compare not only the rates of HF hospitalizations but also in-hospital outcomes. Despite similar demographic characteristics, patients admitted with HF in two referral centers in South London in 2020 experienced worse outcomes compared with those admitted in the previous year (21).

Several studies have reported increased biomarker levels of myocardial injury in COVID-19 patients. The elevation of these markers has been associated with increased disease severity and mortality. These markers include creatine kinase MB subunit (CK-MB), high sensitivity cardiac troponin I (hs-cTnI), interleukin-6, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). About 27.5% of patients who have died from COVID-19 have been shown to have elevated levels of NT-proBNP. Furthermore, 10% of these patients had increased cTnI levels (22).

In patients with heart failure during the COVID-19 pandemic, guideline-directed medical therapy should be continued with additional monitoring. A previous study reported that ritonavir may worsen cardiovascular outcomes in patients with human immunodeficiency virus and heart failure (23). Lopinavir/ritonavir may affect angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and increase sacubitril/valsartan levels, which suggests that close monitoring of blood pressure is necessary. The positive effects of ACEIs/ARBs include ACE2 receptor blockade, disabling viral entry into the heart and lungs, and attenuation of inflammation. However, ACEIs/ARBs may also upregulate ACE2 receptors by a possible retrograde feedback mechanism. There is currently no evidence to suggest that ACEIs/ARBs should be discontinued due to COVID-19 infection.3 Recent publications have shown that ACEIs/ARBs lowered the risk of

all-cause mortality among hospitalized COVID-19 patients with hypertension (24-25).

Digoxin levels should be closely monitored when co-administered with hydroxychloroquine, chloroquine or lopinavir/ritonavir. Eplerenone or ivabradine should not be used with lopinavir/ritonavir because both drugs are mainly metabolized by cytochrome P450 3A4 (CYP3A4). However, spironolactone can be safely prescribed instead. Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase blood pressure and cause fluid retention and should not be used in patients with heart failure (24)

Conclusion

Despite the continued debates about the relation between COVID-19 and HF, there is a lot of evidences about the strong association between them and the impact of the infection on both the morbidity and the mortality of the chronic patients.

References

1. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev. 2005 Dec;69(4):635-64.
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International journal of antimicrobial agents. 2020 Mar 1;55(3):105924.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.
4. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. European journal of heart failure. 2020 Jun;22(6):957-66.
5. Italia L, Tomasoni D, Bisegna S, Pancaldi E, Stretti L, Adamo M, Metra M. COVID-19 and heart failure: from epidemiology during the pandemic to myocardial injury, myocarditis, and heart failure sequelae. Frontiers in cardiovascular medicine. 2021:867.
6. Alvarez-Garcia J, Lee S, Gupta A, Cagliostro M, Joshi AA, Rivas-Lasarte M, Contreras J, Mitter SS, LaRocca G, Tlachi P, Brunjes D. Prognostic impact of prior heart failure in patients hospitalized with COVID-19. Journal of the American College of Cardiology. 2020 Nov 17;76(20):2334-48.
7. Rumery K, Seo A, Jiang L, Choudhary G, Shah NR, Rudolph JL, Wu WC, Erqou S. Outcomes of coronavirus disease-2019 among veterans with pre-existing diagnosis of heart failure. *ESC Heart Fail.* 2021; **8**: 2338–2344.
8. Doolub G, Wong C, Hewitson L, Mohamed A, Todd F, Gogola L, Skyrme-Jones A, Aziz S, Sammut E, Dastidar A. Impact of COVID-19 on inpatient referral of acute heart failure: a single-centre experience from the south-west of the UK. *ESC Heart Fail.* 2021; **8**: 1691–1695.
9. Sokolski M, Trenson S, Sokolska JM, D'Amario D, Meyer P, Poku NK, Biering-Sørensen T, Højbjerg Lassen MC, Skaarup KG, Barge-Caballero E, Pouleur AC. Heart failure in COVID-19: the multicentre, multinational PCHF-COVICAV registry. ESC heart failure. 2021 Sep 17.
10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet. 2020 Feb 22;395(10224):565-74.
11. Faconti L, Chowienczyk PJ, Shah AM. <? covid19?> Cardiovascular disease, heart failure and COVID-19. Journal of the Renin-Angiotensin-Aldosterone System. 2020 May;21(2):1470320320926903.
12. Santos RA, e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, Heringer-Walther S, Pinheiro SV, Lopes MT, Bader M, Mendes EP. Angiotensin-(1–7) is an endogenous ligand

for the G protein-coupled receptor Mas. Proceedings of the National Academy of Sciences. 2003 Jul 8;100(14):8258-63.
13. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. Journal of the American college of cardiology. 2020 Aug 4;76(5):533-46.
14. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, Tobin KA, Cerfolio RJ, Francois F, Horwitz LI. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. bmj. 2020 May 22;369.
15. Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, Kaptein FH, van Paassen J, Stals MA, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research. 2020 Jul 1;191:145-7.
16. De Roquetaillade C, Chousterman BG, Tomasoni D, Zeitouni M, Houdart E, Guedon A, Reiner P, Bordier R, Gayat E, Montalescot G, Metra M. Unusual arterial thrombotic events in Covid-19 patients. International Journal of Cardiology. 2021 Jan 15;323:281-4.
17. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Frontiers in immunology. 2020:1446.
18. Jouline O, Petillot P, Labalette M, Lancel S, Neviere R. Cytokine profile of human septic shock serum inducing cardiomyocyte contractile dysfunction. Physiological research. 2007 Jan 1;56(3):291.
19. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine. 2020 Jul 9;383(2):120-8.
20. Bromage DI, Cannatà A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of the pandemic. European journal of heart failure. 2020 Jun;22(6):978-84.
21. Cannatà A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, Piper S, Shah AM, McDonagh TA. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. European journal of heart failure. 2020 Dec;22(12):2219-24.
22. Lin KC, Wang CC, Huang WC, Hwang JJ. Considerations when managing heart failure during the COVID-19 pandemic-consensus from the Taiwan Society of Cardiology. Acta Cardiologica Sinica. 2021 Mar;37(2):125.
23. Alvi RM, Neilan AM, Tariq N, Awadalla M, Afshar M, Banerji D, Rokicki A, Mulligan C, Triant VA, Zanni MV, Neilan TG. Protease inhibitors and cardiovascular outcomes in patients with HIV and heart failure. Journal of the American College of Cardiology. 2018 Jul 31;72(5):518-30.
24. Dixon DL, Van Tassell BW, Vecchié A, Bonaventura A, Talasaz AH, Kakavand H, D'Ascenzo F, Perciaccante A, Castagno D, Ammirati E, Biondi-Zoccai G. Cardiovascular

considerations in treating patients with coronavirus disease 2019 (COVID-19). Journal of cardiovascular pharmacology. 2020 May 1.
25. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circulation research. 2020 Jun 5;126(12):1671-81.
26. Dassanayaka S, Jones SP. Recent developments in heart failure. Circulation research. 2015 Sep 11;117(7):e58-63.
27. Ohtani T, Mohammed SF, Yamamoto K, Dunlay SM, Weston SA, Sakata Y, Rodeheffer RJ, Roger VL, Redfield MM. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. European heart journal. 2012 Jul 1;33(14):1742-9.
28. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013 Oct 15;62(16):e147-239.
29. Hofmann U, Frantz S. How can we cure a heart "in flame"? A translational view on inflammation in heart failure. Basic research in cardiology. 2013 Jul;108(4):1-9.