Review Article

Arterial Hypertension, Heart Failure, Angina Pectoris, Myocardial Infarction, and Atrial Fibrillation after COVID-19: A Narrative Review

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Abstract

COVID-19 infection is associated with significant complications affecting multiple organs other than the respiratory system. In fact, there seems to be a bidirectional relation between cardiovascular disease and viral infection, as patients with prior cardiac comorbidities are at a higher risk of adverse events during infection, and COVID-19 infection seems to exponentiate the risk of acute and long-term cardiac events. In this review, the authors will discuss the acute and long-term impact of COVID-19 infection in arterial hypertension, heart failure, angina pectoris, myocardial infarction, and atrial fibrillation.

Keywords: Angina pectoris, arterial hypertension, cardiovascular diseases, COVID-19, heart failure, myocardial infarction

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is frequently associated with cardiovascular (CV) complications. A large cohort reported an incidence of acute cardiac events of 11%, disregarding isolated myocardial injury. CV complications were accompanied by an almost two-fold higher risk of severe disease, namely intensive care admission, mechanical ventilation or mechanical extracorporeal support, and inhospital mortality, regardless of preexisting cardiac disease.[1] In another perspective, in addition to older age, underlying CV disease is consistently reported as a risk factor for acute cardiac events, worse prognosis, and increased risk of fatality.[1-4]

In fact, there seems to be a bidirectional relation between CV disease and COVID-19, translated by more serious acute COVID-19 infection in patients with underlying CV disease,[1-4] and increased CV complications observed after severe infection.[5]

After COVID-19 infection, patients are at an increased risk of CV complications,[6-10] and mortality,[6-8] which seems to persist for at least 1 year. Particularly, a large retrospective, matched control study including more than 600,000 COVID-19 survivals reported an increased incidence of major adverse CV events, defined as the composite outcome of myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, heart failure (HF), ventricular arrhythmia, and sudden cardiac death (hazard ratio [HR] = 1.871, 95% confidence interval [CI] = 1.816–1.927), as well as all-cause mortality (HR = 1.614, 95% CI = 1.510–1.703).[6] Accordingly, an analysis of the US Department of Veterans Affairs National Healthcare Database with over 150,000 patients matched with controls presented similar results. Surprisingly, in this cohort, the risk of CV events was largely independent from previous CV disease or classical risk factors such as age, dyslipidemia, diabetes, or hypertension.[7] Additionally, another follow-up cohort of patients hospitalized due to COVID-19 reported that 29%

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required hospital readmission and 12% died 4 months after discharge.[8] On another hand, all these studies consistently concluded that although an increased rate of CV complications seems to persist through the whole COVID-19 disease severity spectrum, both older age and hospitalization during acute infection, in particular intensive care admission, consisted of the main risk factors for adverse outcomes on the long term.[6-8]

It should be noted that the current available evidence regarding COVID-19 infection impact includes patients infected with the early viral strains. This may limit the generalization of these results to more recent strains and particularly after vaccination.

In this review, we will focus on the impact of SARS-CoV-2 infection on arterial hypertension, HF, angina pectoris, MI, and atrial fibrillation (AF). Table 1 resumes the major CV outcomes of COVID-19 infection.

Arterial Hypertension

In the early phase of the pandemic, arterial hypertension was perceived as an important risk factor for SARS-CoV-2 infection adverse outcomes.[37,38] However, adjustment to age and comorbidities, such as obesity and type 2 diabetes, were largely missing. In cohort studies, age is consistently reported as the chief risk factor for severe COVID-19.[15,39,40] Thus, likely the observed association of arterial hypertension with outcomes was not a direct contributing effect of high blood pressure but rather a result of the close epidemiological relation with older age and concomitant comorbidities. At the time being, there is no substantiated evidence to assume that arterial hypertension is directly responsible for infection severity or associated complications.[5,39-41]

New-onset arterial hypertension after COVID-19 infection has been described.[12,14] A cohort study reported new-onset hypertension in 18% of the study population as well as an overall increase in the mean values of systolic and diastolic blood pressure.[11] Another trial enrolling 185 survivals recorded uncontrolled blood pressure in 26% of the patients requiring antihypertensive therapy optimization.[12] In both trials, blood pressure evaluations were performed 1 month after discharge. Likewise, a study with 120 outpatients recovering from mild COVID-19 reported significantly higher systolic and diastolic blood pressures compared with matched controls at 3 months.[13] Moreover, a longitudinal study reported new-onset arterial hypertension in 5 patients and that hypertension was significantly associated with a higher incidence of generalized symptoms.[14] Finally, two retrospective matched control studies, including altogether almost 400,000 COVID-19 survivals, reported a higher risk of developing arterial hypertension 6 months after discharge. Older age and hospital admission during acute infection were identified as risk factors for new-onset arterial hypertension.[9,10]

The mechanism involved in arterial hypertension after SARS-CoV-2 infection is likely due to induced renin–angiotensin–aldosterone system (RAAS) dysregulation. The SARS-CoV-2 enters host cells through the interaction of the spike glycoprotein with the angiotensin-converting enzyme 2 (ACE2) receptor with subsequential internalization of the complex. This interaction promotes the downregulation of the expression of the receptor from the surface cell membrane.[41] The ACE2 receptor cleaves angiotensin 1 into angiotensin 1–9 and angiotensin 2 into angiotensin 1–7 resulting in vasodilation, antiproliferative and anti-inflammatory effects.[42,43] Downregulation of the ACE2 receptor leaves angiotensin 2 effects unopposed with subsequent vasoconstriction, cell proliferation, and increased production of reactive oxygen species and consequent endothelial damage. All these changes will contribute to the development of high blood pressure.[5]

Initial concerns regarding therapy with RAAS inhibitors during acute infection were raised resulting from the hypothesis that these could promote ACE2 membrane expression and therefore increase the susceptibility to SARS-CoV-2 infection.[41] Evidence from observational trials did not support this theory.[44] On the opposite, a protective effect of treatment with RAAS blockers with a reduction in mortality, hospital admission, and transfer to the intensive care unit was even described.[2,45,46] Recent randomized trials suggest a neutral effect of RAAS inhibitors in COVID-19 disease, as shown in an outpatient trial with losartan,[47] in the BRACE-CORONA,[48] or in the REPLACE COVID trial.[49] Considering these results, treatment of arterial hypertension should follow current guidelines and continuation of RAAS blockers is urged by scientific societies as their beneficial effects on the CV and renal system are well-established.[50]

Heart Failure

During COVID-19 infection, acute HF is associated with poor prognosis.[1,16,50] A substantially higher 30-day mortality has been reported compared to infected patients without associated HF (46.8% vs. 19.7%; $P < 0.001$).[16] Accordingly, elevations in the N-terminal pro b-type natriuretic peptide (NT-proBNP) levels have been shown to predict inhospital adverse events.[51]

Different mechanisms may be involved in acute HF including acute myocardial ischemia, myocarditis, stress cardiomyopathy, sepsis cardiomyopathy, tachycardia-induced cardiomyopathy, hypervolemia secondary to acute renal failure, or pulmonary embolism.[50,52] In fact, Rey *et al*. identified dysrhythmias, mainly AF as the strongest predictor of acute HF.[16] Furthermore, the systemic inflammatory state promoted by massive cytokine release is associated with multiorgan dysfunction that may manifest with HF exacerbation ranging from left ventricular dysfunction, pulmonary edema to cardiogenic shock.[53] Incidences of acute HF during COVID-19 infection differ largely among reports with rates from 2% to 23%.[15-17] Woodruff *et al*. reported a 5.4% incidence of acute HF and identified male sex, previous history of HF, AF, and hypertension as the most frequent risk factors for decompensation.[1]

Right ventricular abnormalities, with dilatation or dysfunction, are the most common echocardiographic pathological

Table 1: Summary of the negative cardiovascular consequences of COVID-19

CV consequence	Incidence	Mechanism	Studies
Arterial hypertension			
Long term			
Increased risk of arterial hypertension	18%–26%	Renin–angiotensin–aldosterone system dysregulation	Akpek,[11] De Lorenzo *et al*.,[12] Gameil *et al*.,[13] Nesan *et al*.,[14] Daugherty *et al*.,[9] Cohen *et al*.[10]
HF			
During acute infection			
Acute HF and chronic HF decompensation	2%–23%	Acute myocardial ischemia, myocarditis, stress cardiomyopathy, sepsis cardiomyopathy, tachycardia-induced cardiomyopathy, hypervolemia secondary to acute renal failure, or pulmonary embolism	Woodruff *et al*.,[1] Zhou *et al*.,[15] Rey *et al*.,[16] Vakili *et al*.[17]
Acute right ventricular dysfunction	39%	Increased pulmonary artery resistance due to pulmonary disease, thrombotic pulmonary embolism, cytokine storm, and myocardial damage	Szekely *et al*.,[18] Li *et al*.,[19] Argulian *et al*.,[20] Kim *et al*.[21]
Long term			
HF	-	-	Wang *et al*.,[6] Xie *et al*.,[7]
Cardiomyopathy	-	-	Wang *et al*.,[6] Xie *et al*.,[7] Daugherty *et al*.,[9]
Cardiogenic shock	-	-	Wang *et al*.,[6] Xie *et al*.[7]
Chest pain			
Long term			
Increased incidence of chest pain	2 months - 18%–21% 6 months - 6%–50% 12 months - 7%	-	Carfì *et al*.,[22] Carvalho-Schneider *et al*.,[23] Huang *et al*.,[24] Huang *et al*.,[25] Davis *et al*.,[26] Wang *et al*.,[6] Xie *et al*.[7]
MI			
During acute infection			
Type 2 MI	2.5%	Oxygen supply-demand imbalance due to hypoxemia, systemic inflammation, and adrenergic activation	Stefanini *et al*.,[27] Woodruff *et al*.[1]
MI related complications: Higher thrombus burden, multivessel disease and stent thrombosis, rates of cardiogenic shock, recurrent MI, unplanned angiography, stroke, and inhospital mortality		Prolonged ischemia time due to prolonged symptom onset to hospital presentation and in door-to-balloon times. COVID-19-related prothrombotic and inflammatory state	Kite *et al*.,[28] Garcia *et al*.,[29] Choudry *et al*.[30]
Long term			
Increased MI	-	Endothelial lesion, hypercoagulability, accelerated atherosclerosis due to pro-inflammatory state and use of immunosuppressive agents, depression, and disease-induced sarcopenia	Wang *et al*.,[6] Xie *et al*.[7]
AF			
During acute infection			
Increase burden of AF	15%–20%	Direct myocardial cell invasion, pro-inflammatory and thrombotic state, endothelial damage, hypoxemia, and sympathetic system activation	Coromilas *et al*.,[31] Gopinathannair *et al*.,[32] Peltzer *et al*.,[33] Musikantow *et al*.,[34] Colon *et al*.,[35] Spinoni *et al*.,[36]
New-onset AF	~10%		Peltzer *et al*.[33]
Long term			
Increase incidence of AF	-	-	Wang *et al*.,[6] Xie *et al*.[7]

AF=Atrial fibrillation, HF=Heart failure, MI=Myocardial infarction, CV=Cardiovascular

findings during acute viral infection.[18] Right ventricular abnormalities likely result from increased pulmonary artery resistance in the setting of pulmonary disease, thrombotic pulmonary embolism,[18] cytokine storm, and myocardial damage. Furthermore, right ventricular remodeling was associated with increased mortality.[19-21] Indeed, a two-fold

increased risk of mortality was observed after adjustment for clinical and analytical variables in a large cohort.[21] However, another study reported reduced right ventricular strain as the best echocardiographic predictor of inhospital death, invasive ventilation, and acute HF.[19] The ECHOVID-19 study concluded that both left and right ventricular dysfunctions, assessed by left global longitudinal strain, tricuspid annular excursion, and right ventricular strain, were significantly more impaired in comparison to controls and associated with inpatient mortality.[54] Nevertheless, these results should be carefully interpreted as prior HF, chronic pulmonary disease, type 2 diabetes, and dyslipidemia were significantly more prevalent in COVID-19 patients compared to controls. In the follow-up study, cardiac biomarkers normalized and the right ventricular parameters and left global longitudinal strain improved to values within normal cutoffs.[55]

Regarding patients with chronic HF, these are at a higher risk of acute HF decompensation,[1,16,50] hospitalization, and poor outcomes with longer lengths of hospital stay,[56] increased risk of mechanical invasive ventilation, and higher mortality.[2,16,56,57] In a large trial including close to 9,000 patients, congestive HF was reported as an independent predictor of inhospital death (15.3% vs. 5.6%, HR = 2.48 [95% CI = 1.62–3.79]).[2] Chatrath *et al*. analyzed the impact of COVID-19 concomitant infection in 140 patients with chronic HF admitted for acute HF decompensation. A significant increase in acute kidney injury, myocardial injury, superadded bacterial infection, and inpatient death was observed, reaching an impressive mortality of 50% versus 10% in non-COVID-19 patients.[57] Reduced left ventricular ejection fraction is possibly also associated with worse outcomes, with higher rates of cardiogenic shock and hospital readmission at 30 days.[56]

In chronic HF patients, guideline-directed medical treatment should not be withdrawn unless it becomes medically necessary due to hypoperfusion or renal deterioration.[50] In fact, an observational study demonstrated increased inhospital fatality associated with HF therapy withdrawal.[16] Nevertheless, the reasons for HF therapy discontinuation are unclear and it should be questioned whether these patients did not present an acute severe clinical status that led to HF therapy intolerability and that may have directly impaired prognosis. In conclusion, all efforts should be made to resume HF foundational therapy shortly after clinical stabilization.

Initial cardiac magnetic resonance reports described cardiac involvement in up to 80% of COVID-19 patients, with increased myocardial edema and late gadolinium enhancement, mainly with a nonischemic pattern.[58] These raised relevant concerns on the development of future substrate for HF and arrhythmia. However, results from cardiac magnetic resonance in COVID-19 are not consistent. After mild infection, a 2.8% incidence of cardiac magnetic resonance suggestive of myocarditis was observed in a large study with over 1,500 athletes,[59] as well as an incidence of myocarditis-like enhancement of 4% in another cohort 6 months after COVID-19 recovery comparable to healthy controls.[60] Moreover, a prospective longitudinal study of 31 patients who underwent cardiac magnetic resonance before AF ablation and 5 months post-COVID-19 infection revealed no difference regarding left ventricular function or *de novo* late gadolinium enhancement lesions. It is worth noting that none of these patients reported cardiac symptoms and only 9 (29%) required hospital admission, and thus, these results may not be generalized to patients with CV decompensation associated with COVID-19 patients.[61]

On the long term, a matched control cohort with more than 600,000 patients reported an increased incidence of HF (HR = 2.296, 95% CI = 2.200–2.396), cardiomyopathy (HR = 2.413, 95% CI = 2.235–2.606), and cardiogenic shock (HR = 1.988, 95% CI = 1.599–2.473).[6] Accordingly, in the veteran longitudinal cohort, an increased risk of HF with a HR of 1.7 (95% CI = 1.65–1.80) was observed and associated with a substantial HF burden (11.61 [10.47–12.78] per 1,000 patients).[7] In another large retrospective cohort, the risk of new cardiomyopathy was about 2.5 higher in postacute COVID-19 patients in comparison to a matched healthy cohort, but interestingly, no difference was found in comparison with the previous viral lower respiratory tract infection group.[9] Unfortunately, in none of these trials, details regarding HF etiology, New York Heart Association clinical status, NT-proBNP, or echocardiographic parameters were provided.

On the other hand, the negative impact of the COVID-19 pandemic extends well beyond infected patients. During the state of emergency, medical care was largely compromised, conditioning the reduction of HF diagnosis, specialized follow-up appointments of chronic HF patients, with a major impact on the ability to optimize medical therapy or prevent HF decompensation. Although a reduction in the absolute number of acute HF hospitalizations was reported, admitted patients were in more deteriorated conditions with more advanced NYHA functional classes.[62] Additionally, increased 30-day hospital readmission and inhospital mortality (7.3% vs. 6%, $P = 0.002$) were reported.[63] Another evidence of the global negative impact of the pandemic is shown by a 4-fold increased incidence of stress cardiomyopathy compared to prepandemic (7.8% vs. 1.5%–1.8%, respectively) in patients with negative reverse transcription–polymerase chain reaction (RT-PCR) tests.[64]

Chest Pain

Chest pain is among the most frequently reported CV symptoms in postacute COVID-19. Two trials evaluated postacute COVID-19 symptoms at 60 days, detecting chest pain in 18%–21% of the population.[22,23,65] Moreover, Huang *et al*. reported chest pain incidence of 5% at 6-month follow-up[24] and 7% at 12 months after discharge[25] and was independent of acute infection severity. Consistently, in a large systematic review of postacute COVID-19 sequelae, chest pain was the most reported symptom at 6 months, with an average prevalence of 13%.[66] However, in an international survey,

chest pain was described with an impressive rate exceeding 50% of the survivals.[26]

Two controlled cohorts published data regarding angina. In a large database, Wang *et al*. reported an increased risk of angina at 12 months with an HR of 1.707 (95% CI = 1.545–1.885) in comparison with a matched cohort.[6] And likewise, in the veteran database analysis, a 1.5-fold increased risk of angina was reported at 12 months.[7]

Nevertheless, the correlation of symptoms with results from ischemic tests or coronarography anatomic details is missing in the literature.

Myocardial Infarction

Myocardial injury was frequently reported during acute COVID-19 infection with an estimated rate between 7%–70%.[3,4] The magnitude of serum troponin elevation seems to be directly related to severe disease severity including inhospital mortality.[3,5,67] Myocardial injury was also more commonly reported in patients with previous CV comorbidities – acute coronary heart disease (29.3% vs. 6.0%) and chronic HF (14.6% vs. 1.5%).[67] Nevertheless, it remains unknown whether this troponin rise represents solely a marker of severe disease or itself contributed to a more adverse prognosis.[3]

In similarity with other viral infections, COVID-19 infection may directly trigger MI, both type 1 MI with atherosclerotic plaque rupture promoted by enhanced systemic inflammation and immune system activation[3,68] or type 2 MI.[3] Type 2 MI due to imbalance in the oxygen supply–demand without coronary thrombosis resulting from hypoxemia, systemic inflammation, and adrenergic activation is more likely to occur.[44,49] Accordingly, an elevated prevalence of nonobstructive MI was observed in a study with patients undergoing coronarography for ST-segment elevation MI (STEMI) in which 40% of the patients had no identifiable culprit lesion.[27] Likewise, a large cohort of acute CV complications of COVID-19 reported acute ischemic heart disease in 5.5% of the patients where type 2 MI had a significant preponderance of the cases occurring in 2.1%. The main predictors of acute ischemic disease were older age, male sex, prior arterial hypertension, valvular cardiomyopathy, and chronic kidney disease.[1]

Acute coronary syndrome medical care was significantly hindered during the pandemic. At first, a significant decrease of inhospital presentation was reported with a considerable decrease in rates of acute coronary syndrome in comparison to prepandemic years.[69] Moreover, significant prolonged times in symptom onset to hospital presentation[28,70] and in door-to-balloon were registered in STEMI.[28] Importantly, COVID-19 patients were more likely to be treated with medical treatment rather than invasive emergent angiography compared to standard care.[29] The combination of prolonged ischemia time, driven by delayed angioplasty and medical therapy, well recognized to negatively impact clinical outcomes, together with the prothrombotic and inflammatory state induced by COVID-19 infection, were likely responsible for the worsen clinical outcomes during the pandemic. Accordingly, two multicenter studies reported higher inhospital complications with increased rates of cardiogenic shock, recurrent MI, unplanned angiography, stroke, and inhospital mortality compared to previous years.[28,29] Additionally, higher thrombus burden, multivessel disease, and stent thrombosis in comparison with non-COVID-19 MI patients were described.[30]

Viral infection by COVID-19 is associated with a micro-inflammatory state and dysregulation of the immune system which results in endothelial lesion and accelerated atherosclerosis.[68] Additionally, hypercoagulability, induced or accelerated dyslipidemia by immunosuppressive agents, depression, and disease-induced sarcopenia contribute to CV risk factors. Adding altogether sets COVID-19 survivals at a high risk of vascular events.[71]

A systematic meta-analysis gathered the evidence from four large data-based matched control cohorts including over 1.2 million COVID-19 survivals.[6,7,9,10] After a mean follow-up of 8.5 months, acute MI occurred in 3.5 versus 2.02 cases per 1,000 patients in postacute COVID-19 compared to controls, representing a 93% excess risk of suffering an acute MI. A significant correlation with age and male gender was observed and indirectly with length of hospital stay.[72] Information concerning clinical presentation, rate of MI with ST-segment elevation, treatment approach, complications, and outcome were not provided.

Atrial Fibrillation

Consistent with other CV diseases, preexisting AF is associated with adverse outcomes after acute viral infection with increased mortality.[73]

Supraventricular arrhythmias, and particularly AF, are the most frequently documented arrhythmia, with reported rates between 15% and 20% during acute COVID-19[31-33] and new-onset AF ~10%.[33] This incidence is similar to the one reported during other viral infections such as influenza infection and acute respiratory distress syndrome.[34,74]

Age and comorbidities are risk factors for AF during COVID-19 infection.[33,34] Additionally, AF was associated with increased levels of cardiac biomarkers and adverse clinical outcomes, with intensive care unit admission, mechanical ventilation, and vasopressor support and mortality.[33,35,36] Particularly, new-onset AF was reported as a predictor of inhospital mortality and severe COVID-19 infection.[36]

Acute SARS-CoV-2 infection may predispose to the risk of AF through different pathological pathways that likely contribute to atrial electrical imbalance, such as direct myocardial injury, pro-inflammatory state, hypoxemia, and sympathetic system activation.[75]

Nevertheless, whether a definite causal association exists between COVID-19 infection and AF is controversial. This was explored in a large Mendelian randomized study using

Genome-wide association studies data, where no definite relation between AF and COVID-19 infection or disease infection was detected.[76]

Importantly, the long-term clinical impact of COVID-19-associated AF, AF recurrence, and rates of progression to permanent AF remain unknown.

In 1-year follow-up among COVID-19 cohorts, AF is the most frequently reported arrhythmia, increasing two-fold the risk compared to matched controls.[6,7] The risk of AF was proportional to the severity of acute COVID-19 infection.[7]

Conclusion

Acute SARS-CoV-2 infection has significant implications for CV health and deserves appropriate clinical and scientific follow-up. There is an evident bidirectional relationship between COVID-19 and CV disease, as patients with preexisting cardiac conditions pose a higher risk of severe COVID-19 infection and increased CV complications during infection. On the other hand, COVID-19 survivors are also at elevated risk of developing CV complications and experiencing adverse outcomes in the long term.

Therefore, further research is needed to clarify the real long-term impact of CV complications associated with COVID-19 infection. A better understanding is crucial to implement appropriate screening strategies for optimizing the care and outcomes of COVID-19 survivals.

Author contributions

Joana Brito designed the study and wrote the first draft of the manuscript with Daniel Caldeira, Catarina Gregório, Rui Plácido, and Fausto J Pinto. Each co-author contributed to either the delivery of the study or helped with the writing. All authors have given final approval for the current version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Prof. Fausto J. Pinto is an Editorial Board member of *Heart and Mind*. The article was subject to the journal's standard procedures, with peer review handled independently of Prof. Fausto J. Pinto and the research group. There are no conflicts of interest.

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