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COVID-19 and the Heart

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Abstract

An outbreak of coronavirus disease 2019 (COVID-19) occurred in December 2019 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a strain of SARS-CoV. Patients infected with the virus present a wide spectrum of manifestations ranging from mild flu-like symptoms, cough, fever and fatigue to severe lung injury, appearing as bilateral interstitial pneumonia or acute respiratory failure. Although SARS-COV-2 infection predominantly offends the respiratory system, it has been associated with several cardiovascular complications as well. For example, patients with COVID-19 may either develop type 2 myocardial infarction due to myocardial oxygen demand and supply imbalance or acute coronary syndrome resulting from excessive inflammatory response to the primary infection. The incidence of COVID-19 related myocarditis is estimated to be accountable for an average of 7% of all COVID-19 related fatal cases, whereas heart failure (HF) may develop due to infiltration of heart by inflammatory cells, destructive action of pro-inflammatory cytokines, micro-thrombosis and new onset or aggravated endothelial and respiratory failure. Lastly, SARS-COV-2 can engender arrhythmias through direct myocardial damage causing acute myocarditis or through HF decompensation or secondary, through respiratory failure or severe respiratory distress syndrome. In this comprehensive review we summarize the COVID-19 related cardiovascular complications (acute coronary syndromes, myocarditis, heart failure, arrhythmias), and discuss the main underlying pathophysiological mechanisms.

Key Words: COVID-19; Virus; complications; Cardiac; Acute coronary syndromes; Heart failure; Myocarditis; Arrhythmias

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Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 disease. Although SARS-COV-2 infection predominantly offends the respiratory system, it leads to various cardiovascular complications as well. SARS-COV-2 infected patients with a history of cardiovascular disease exhibit poor outcomes. The main COVID-19 related cardiovascular complications include acute coronary syndromes, myocarditis, heart failure, and arrhythmias.

INTRODUCTION

A global outbreak of coronavirus disease 2019 (COVID-19) occurred in December 2019 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Patients susceptible to the virus present a wide spectrum of manifestations ranging from mild flu-like symptoms, cough, fever and fatigue to severe lung injury, appearing as bilateral interstitial pneumonia or acute respiratory failure [3]. The majority of COVID-19 patients who progress to critically ill tend to have mild symptomatology in the early phase of the disease. The condition of these subjects abruptly worsens in the later phases of the disease or in the recovery process, usually due to "cytokine storm" and acute lung injury (acute respiratory distress syndrome/ARDS) [4]. In general, acute respiratory syndromes can be divided in those stemming from direct lung injury factors (i.e. bacterial, viral or fungal pneumonia) and those from indirect lung-injury risk factors (i.e. sepsis, hemorrhagic shock or pancreatitis) [5]. Until now more than 50 million people worldwide have been infected with the virus, while it has been considered responsible for more than 2.230.000 deaths [6, 7]. Recent literature indicates that SARS-COV-2 infected patients with a history of cardiovascular disease display increased mortality. Patients with a history of hypertension, diabetes, obesity are also considered frail [8, 9]. Additional risk factors are senility, chronic renal dysfunction, chronic respiratory diseases and concomitant malignancies [10]. Although SARS-COV-2 infection predominantly offends the respiratory system, it is liable for various cardiovascular complications as well. The usual management of patients with COVID-19 includes self-isolation and supportive measures (antipyretics, rehydration)

in mild cases (absence of signs of severe or critical disease), and hospitalization in severe (oxygen saturation < 90%on room air, signs of pneumonia, signs of respiratory distress) and critical cases (requires life sustaining treatment, acute respiratory distress syndrome, sepsis and septic shock) [11]. In this comprehensive state of the art review, we will attempt to summarize COVID-19 related cardiovascular complications, with a special concern in enlightening the subjacent mechanisms and pathophysiological traits below the main cardiovascular manifestations.

2. PATHOPHYSIOLOGY OF COVID-19 INFECTION

The affinity of SAR-COV-2 infection to ACE-2 receptor has been proposed to be the core of the disease's pathophysiology, since it not only causes cardiovascular complications but also propagates disproportionately in cases with a pre-existing cardiovascular impairment [12]. ACE-2 is a membrane bound carboxypeptidase. Its normal function is to convert Ang II to Ang (1-7) and ANG I to Ang (1-9) [4]. After being enzymatically cleaved at sites S1/S2 by protease furin and at S2' region by serine protease TMPRSS2, SARS-COV-2 anchors its surface glycoprotein spike (S) to ACE-2 to create its path to the host cells (Figure 1) [13].

Except for the transmembranic ACE-2 the receptor can also be found in a much smaller concentration in a soluble form, no longer being able to mediate SARS-COV-2 endocytosis, after being seceded by the cell membrane by metalloproteinase ADAMTS17 [14]. TLR-4 is a transmembranic receptor present on the surface and in the endosomes of host cells, such as macrophages and dendritic cells, that recognizes damage associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) released by neighboring tissue after cell damage [15]. After its activation it can trigger the release of proinflammatory cytokines as well as the release of anti-inflammatory cytokines and interferons. It has been proposed that its activation facilitates the expression of ACE2 receptors, participating in that way in a vicious cycle of cytokine storm establishment. Moreover, its activation on platelets induces a

prothrombotic and procoagulant state, offering a conceivable explanation for the thrombogenic state in COVID-19 set [16]. Except for the suggested contribution of ACE-2 to the disease's commence, additional receptors that could mediate the entry of SARS-COV-2 in human cells is the recently recognized family of CD209. S viral glycoproteins present an elevated affinity to these sites and is postulated that it could be effective for viral entry even in the absence of ACE-2. Ectopically expressed CD209 receptor could also intercede with viral entry [17]. Other receptors that interact with SARS-COV-2, indicating additional possible routes for infection are MR/CD206, MGL/CLEC10A/CD301 [18]. Variation in the above mentioned receptors as well as in genes expressing priming proteases such as Transmembrane Protease Serine 2 (TMPRSS2), Cathepsin B (CTSB), Cathepsin L (CTSL) could provide a possible explanation for the diversity in infection susceptibility and range of symptoms in different individuals [19].

3. COVID-19 AND CARDIOVASCULAR DISEASE

3.1. COVID-19 and acute coronary syndromes

Despite the elevated incidence of myocardial infarction in COVID-19 patients, a substantial drop in the number of patients (up to 40%) addressing the emergency department due to acute coronary syndromes (ACS) has been observed in several countries, especially in the early stages of the pandemic. [20] [21] [22]. In Greece, a country which implemented strict social measures, a reduction of approximately 30% in ACS hospitalizations during the COVID-19 outbreak was reported along with no excess in in-hospital mortality [23]. Several explanations for this trend have been proposed such as the poor participation in aerobic exercise, the reduction in air pollution as well as the changes in lifestyle and diet associated with the pandemic environment, or the fact that patients with less severe symptoms are reluctant to visit the hospital [24]. Several studies have reported the significant reduction in the total number of urgent and emergent coronary angiography performed in patients with ACS during the COVID-19 pandemic. COVID-19 patients with STEMI often did not receive guideline-

recommended treatments, while the use of fibrinolysis over primary percutaneous coronary intervention (PCI) has been reported in a high number of cases [21, 25-28]. However, an analysis from the Beijing Inpatient Database Study reported that the proportions of patients with ACS receiving PCI, the proportion of patients with STEMI receiving PCI within 24 h, and the proportion of patients with unstable angina receiving coronary artery bypass graft (CABG) were higher in the study period (December 1, 2019 to June 30, 2020,), compared to those in the control period (December 1, 2018 to June 30, 2019) [29].

The cardiac involvement of COVID-19 as demonstrated by increased troponin levels at hospital admission has been associated with adverse prognosis in several cohorts [30, 31]. A recent study by Nuzzi *et al* demonstrated the prognostic significance of troponin trajectories in hospitalized patients with COVID-19 [32]. The authors reported that the strongest independent predictor of increased mortality was the presence of normal troponin at admission and elevated troponin (defined as values above the 99th percentile of normal values) on day 2 (hazard ratio 3.78, 95%confidence interval 1.10–13.09, $P = 0.035$). The aforementioned study suggests that COVID-19 patients deserve a serial troponin assessment, beyond baseline values, because it may have an additive prognostic role.

It is proposed that two different groups of COVID-19 patients with ACS exist. The first group includes patients with pre-existing atherosclerosis, a history of heart failure (HF) or multiple cardiovascular risk factors, who are prone to develop acute myocardial injury. Systemic hypoxia in patients with severe pneumonia or ARDS along with increased metabolic demands can precipitate imbalance between myocardial oxygen demand and supply, leading to type 2 myocardial infarction. Meanwhile, hypoxia-induced influx of calcium ions also leads to injury and apoptosis of cardiomyocytes [33]. Therefore, not surprisingly hypoxemia (defined as pulse oximetry <96%) has been reported to be an independent risk factor of ACS development in COVID-19 patients [34]. Moreover, it is well recognized that sepsis increases the risk for cardiovascular events and the risk of myocardial injury is linearly associated to the severity of

respiratory infectious diseases [35].

In the second group the excessive inflammatory response to the primary infection is the main mechanism. Patients may lack previous cardiovascular history or classic risk factors for coronary disease. Coronary occlusion occurs in the setting of procoagulant state and excessive autoimmune response [36, 37]. Such patients are usually sick for at least two weeks with SARS-CoV-2, and ACS develops against the background of this infection [38]. A Swedish study which included 86 742 patients with COVID-19 and 348 481 matched control individuals reported an increased risk of myocardial infarction in COVID patients the first 2 wk after the infection [39]. In an observational study of 119 SARS-COV-2 positive patients presenting with COVID-19 a high thrombus burden evidenced with coronary thrombus, multivessel thrombosis and stent thrombosis during initial catheterization were observed [40]. In this case, patients are more often in need for thrombus aspiration, use of glycoprotein IIb/IIIa inhibitors and higher levels of heparin in order to achieve standard ACT levels [41]. Nonetheless the two groups may share common pathophysiological mechanisms (Figure 2). Multiple microthrombosis and endothelial dysfunction can complicate the clinical course in critically ill patients with sympathetic activation and increased metabolic demand and also in patients with high thrombus burden of epicardial coronary arteries as well. Coronary spasm and vasculitis-like vessel damage can occur in both groups [42].

Systemic inflammatory response due to cytokine storm can destabilize preexisting atherosclerotic plaques in patients with atherothrombosis, leading to rupture and subsequent excessive thrombus formation [43]. Below we discuss the main mechanisms associated with thrombosis and immune response presented in COVID-19 patients with ACS.

3.1.1 Viral mediated thrombosis

The occurrence of exacerbated thrombotic events in viral infection is not a novel concept. Immunopathological process in viral infections with influenza virus, SARS-COV-1, MERS have been reported and attributed mainly to cytokine release syndrome.

Secretion of proinflammatory cytokines IL-1, IL-6, TNF-a, TNF-γ are postulated to aggravate myocardial function acutely and subacutelly through the secretion of neural sphingomyelinase and *via* nitric oxide-mediated blunting of beta-adrenergic signaling [44, 45]. The core mechanisms responsible for myocardial injury is the disruption of endothelial integrity, the interaction of immune cells, mainly leukocytes, with coagulation factors and platelets, the constant secretion of cytokines and the release of prothrombotic mediators, such as tissue factor (TF) (Figure 3) [46]. Both enveloped and non-enveloped viruses are capable of mediating thrombosis mainly through up regulation of the extrinsic coagulation pathway, as demonstrated in former assays where respiratory viruses induced a 4-5 fold increase in TF and Xa factor and reduced the clotting time by 55% [47]. Similarly, herpes virus and measles virus induce procoagulant activity by increasing the affiliation of leukocytes and monocytes to endothelial monolayers [48, 49]. Myocardial injury encountered at patients infected with SARS-COV-2 resembles that caused by SARS-COV-1, influenza virus and MERS-COV. In a former study it was demonstrated that patients infected with influenza present a six fold elevated risk of having a myocardial injury (both STEMI and NSTEMI) during the illness seasons. Nevertheless, COVID-19 infection has been associated with a significantly higher incidence of myocardial infarction compared to influenza. Moreover, patients infected with SAR-COV-2 have elevated levels of prothrombotic factors compared to other viral infections. ICAM1, VCAM1, P-selectin, sCD40L and thrombomodulin are highly expressed during the disease's procession [50].

3.1.2. Immune response in acute myocardial infarction

Ischemic injury after acute myocardial infarction mobilizes a wide range of immune responses of innate and adaptive immunity. The progress commences with the release of preformed granules of resident mastic cells which induces the release of inflammatory cytokines and chemokines of the macrophages and endothelial cells. After that, neutrophils and macrophages mainly from the hematopoietic stem and progenitor cells (HSPCs) in the bone marrow, infiltrate the cardiac muscle in a biphasic response, sequencing the inflammatory cascade [51]. Leukocytosis itself, although it

starts initially as a compensatory mechanism for the preservation of cardiac muscle integrity, constitutes an independent cardiovascular risk factor. The absolute balance of the immune response is crucial for the outcome of the disease, since an over-accumulation of immune cells in the early stages leads to thinning of the infarct tissue while an absence of a vigorous immune response can lead to an excess of granulation tissue, making myocardial wall less stable and prone to rupture. Acute deregulation of the immune system in SARS-COV-2 infected patients can amplify immune response and precipitate multiple organ failure as well as acute myocardial infarction [52].

3.1.3. NETosis

Another recently studied pathway of immunothrombosis in COVID-19 is associated with the formation of neutrophil extracellular traps (NETs). In response to certain stimuli, neutrophils enhance their antimicrobial activities by releasing NETs, composed of extracellular chromatin [53]. Attached to these web-like DNA structures are histones and granule proteins such as myeloperoxidase (MPO), as well as cytosolic proteins. Activated neutrophils release nuclear DNA into the extracellular environment, where it can trap and neutralize pathogens. This process is termed NETosis [53]. Beyond the primarily propitious impact of these structures to the confinement of the inflammation, a parallel unfavorable effect to thrombus formation has been demonstrated. It has been suggested that NETs provide the scaffold for fibrin deposition and platelet entrapment and subsequent activation [54]. Subsequent platelet activation assisted by histones, also a key segment of NETs structure, leads to a vicious cycle with an end point the endothelial injury and the impairment of blood flow [54, 55]. In addition to platelet entrapment and activation, NETs' contribution to vascular thrombus formation is also mediated through erythrocytes entrapment and fibrin deposition [56]. The contribution of NETs to vascular thrombogenesis is further supported by the presence of TF on NETs. More specifically it was demonstrated that neutrophils in an inflammatory substrate released large amounts of TF and subsequently generated thrombin and concluded in platelet activation [57]. In a prospective cohort study of 33 COVID-19 patients and 17 sex-matched controls, NETs, Platelet Factor U and selected

cytokines were measured and correlated directly with illness severity [58]. Lastly, in another study of 84 sera samples highly specific markers of NETs –MPO-DNA, citrullinated Histone 3 (Cit-H3) were reported at COVID-19 patients' sample and directly correlated to acute phase reactants, CRP, D-dimmers and lactate dehydrogenase [59].

3.2. COVID-19 AND MYOCARDITIS

3.2.1. COVID-19 related myocarditis

Acute myocarditis has been reported as a possible complication in SARS-COV-2 positive patients. Intracellular SARS-CoV-2 might impair stress granule formation *via* its accessory protein. Without the stress granules, the virus is allowed to replicate and damage the cell. Naïve T lymphocytes can be primed for viral antigens *via* antigen-presenting cells and the heart-produced hepatocyte growth factor. The primed CD8+ T lymphocytes migrate to the cardiomyocytes and may cause myocardial inflammation through cell-mediated cytotoxicity [60]. SARS-CoV-2 may also bring about myocardial damage *via* the infection of endothelial cells in the heart. This theory is reinforced by the histological discovery of SARS-CoV-2 in endothelial cells of several organs, including the heart [61].

The incidence of COVID-19 related myocarditis is estimated to be accountable for an average of 7% of all COVID-19 related deaths [60]. However COVID-19 related mortality displays a varying prevalence among different population groups. Increased troponin levels in COVID-19 are related to adverse outcomes, but the specific prognostic role of myocarditis is not known [62]. The clinical spectrum of SARS-COV-2 myocarditis is relatively wide. Patients may present with symptoms of thoracic pain, fever and tachycardia. A retrospective cohort from 23 hospitals in the United States and Europe revealed chest pain and dyspnea as the most common symptoms at admission, whereas the majority of acute myocarditis occurred in the absence of pneumonia [63]. Patients with concomitant myocarditis and pneumonia exhibited the worse prognosis at 120 days. In more severe cases dyspnea and fatigue may be encountered. In an advanced clinical course patients may develop HF and cardiogenic shock. Signs and symptoms of

right HF may also be encountered, with peripheral edema and jugular veins distention being the initial clinical manifestation [60]. Fulminant myocarditis, although uncommon, has also been reported as a complication secondary to COVID-19 infection [64]. In such occasion cardiogenic shock may develop rapidly while the patient is at risk of fatal ventricular tachyarrhythmia or bradyarrhythmia [65]. Additionally, patients with COVID-19 myocarditis are at the risk of ventricular and supraventricular arrhythmias. Arrhythmogeneity is attributed to re-entrant arrhythmias originating from scars and pro-inflammatory cytokines-mediated conduction disorders [66].

Skeletal muscle myopathy is an extra-pulmonary manifestation of COVID-19, observed in approximately one-third of symptomatic patients and varying from limited myalgia to myositis or rhabdomyolysis. A case series of patients with concurrent myopathy and inflammatory cardiac disease secondary to active COVID-19, revealed that the majority of patients were lacking of a major respiratory complication, whereas only two subjects experienced critical COVID-19 pneumonia [67].

The differential diagnosis includes COVID-19 related acute coronary syndromes, cardiomyopathy in the status of multiorgan dysfunction syndrome and Takotsubo cardiomyopathy. Elevated troponin levels accompanied by acute chest pain insinuate non-STEMI as the predominant situation. Predisposing factors of coronary heart disease such as dyslipidemia, arterial hypertension, family history and comorbidities should be scrutinized. In high suspicion of ACS, epicardial disease has to be ruled out by coronary angiography. Sepsis-induced myocardial dysfunction in intensive care units ranges from 10 to 70% between studies [68]. Stress induced cardiomyopathy incidence appears to be elevated between human-coronavirus positive patients. A recent study demonstrated a substantial rise in the incidence of stress cardiomyopathy during the COVID-19 period (7.8%), compared to prepandemic timelines (1.5%-1.8%) [69, 70]. Reverse Takotsubo cardiomyopathy has also been reported as the first direct evidence of myocardial inflammation in a woman with interstitial inflammatory lung disease due to COVID-19 [71].

In the setting of high clinical suspicion of COVID-19 associated myocarditis the

diagnostic evaluation is based on the application of cardiac imaging methods – echocardiogram and cardiac magnetic resonance imaging (CMR) [65]. Echocardiographic signs of myocarditis depend on disease's severity and include wall motion abnormalities, increased wall thickness, mildly or severely reduced myocardial contractility, cardiac chamber dilatation and pericardial effusion. In mild forms, echocardiographic evaluation may be otherwise normal, except for reduced myocardial strain. CMR imaging in myocarditis evaluation is usually applied early after the disease in order to denote the extend of myocardial injury. Myocardial edema and scarring have been reported in the majority of patients with COVID-19 myocarditis [72]. Cardiac computed tomography (CT) scan with contrast enhancement can be utilized when CMR is unavailable or contraindicated [73].

Currently, treatment for viral myocarditis is largely supportive. When left ventricular (LV) systolic dysfunction occurs, heart failure therapy is recommenced (i.e. angiotensin-converting enzyme-inhibitors and b-blockers) in a patient with sufficient cardiac output and haemodynamic stability. Several ongoing trials are investigating immunosuppressant therapy for the hyperinflammatory phase that may be useful to COVID-19-related myocarditis [62].

3.2.2. COVID-19 vaccine-associated myocarditis

Vaccination against SARS-COV-2 has been anticipated worlwide as the redemption of the pandemic. Although overly infrequent, myocarditis has been discerned as a potential side effect of COVID-19 mRNA-vaccines [74]. COVID-19 mRNA-vaccine-associated myocarditis incidence is estimated to 0.3-0.5 per 100.000 vaccinated people, which is significantly lower than the incidence of acute viral myocarditis (1–10 per 100,000 people per year) or COVID-19-related myocarditis or myocardial injury (1-4% of infected patients) [75]. In addition to its low incidence, mRNA-related myocarditis displays a favorable prognosis, with >80% recovery and >99% survival [76]. Among those who will present with vaccine-related myocarditis, an increased possibility of myocarditis during the first week after the second dose of mRNA vaccines have been observed. The population group mostly affected, seems to be young men [77]. In

immunogenic susceptible patients vaccine-associated myocarditis constitutes the manifestation of hyperimmunity of the preceded sensitization to the virus. SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA encapsulated in lipid nanoparticles which, after the entrance in host cells drives the translation of the receptor binding spike glycoprotein of the virus [78]. Spike glycoprotein encoded by the vaccine mRNA stimulates the attraction of specific IgG antibodies and causes the activation of the acquired immune response, which has been adapted after the first vaccination dose. Hyperimmunity in genetically susceptible patients can activate proinflammatory cascades and stimulate an amplified immune response [79]. Molecular mimicry between cardiac muscle segments and the spike protein of SARS-COV-2 is another potential mechanism [75]. Myocardial α-myosin heavy chain which is structurally similar to SARS-COV-2 spike glycoprotein can be falsely identified as antigens and be objected by preformed antibodies [78]. However, new-onset myocardial injury following vaccination cannot be entirely attributed to cross reaction between self-antigens, letting this be the case only in immunogenetically predisposed patients. The suggested pathophysiological mechanism to interpret the divergence in the incidence of vaccine-induced myocarditis between male and female patients lies in the differentiation in hormone signaling. Elevated testosterone levels are associated to inhibition of anti-inflammatory cells and predominance of Th-1 type response. Estrogen, on the other hand, seem to have a protective role, inhibiting the action of pro-inflammatory T cells and being associated with a prevalence of anti-inflammatory elements such as increased B cells, IL-10, domination of T regulatory cells and M2 macrophage activation pattern. [76].

3.3. COVID-19 AND HEART FAILURE

HF has been acknowledged as one of the most common critical complications during COVID-19 pandemic along with acute cardiac injury, sepsis and acute respiratory distress syndrome [80]. COVID-19 patients may develop HF due to infiltration of heart by inflammatory cells, destructive action of pro-inflammatory cytokines, micro-thrombosis and new onset or aggravated endothelial dysfunction and respiratory

failure [81]. SARS-COV-2 is accountable for viral inclusions in myocardium and the consequent infiltration by monocytes/macrophages, neutrophils, and lymphocytes [82]. COVID-19 related myocarditis may progress to dilated cardiomyopathy and advanced HF with reduced ejection fraction [83, 84]. Other possible mechanisms include a) cor-pulmonale secondary to ARDS or pulmonary embolism, b) the use of steroids which can cause fluid overload, and c) the administration of cardiotoxic drugs (i.e. hydroxychloroquine or azithromycin) [85].

Patients with HF hospitalized for COVID-19 exhibit a particularly increased risk of in-hospital complications and excess mortality. HF and SARS-COV-2 infection share common risk factors such as senility, lung disease, chronic kidney disease and hypertension [86]. As reported in a retrospective study of 2,184 patients hospitalized with COVID-19, the sub-group of HF experienced a longer hospitalization, and developed more frequently myocardial infarction or shock. [87]. Likewise, in a retrospective, multicenter study including 1,718 patients with HF, hospitalized for COVID-19 the overall fatality rate was 47.6%. This remarkably elevated disease burden was correlated with older age, tachycardia, raised CRP and serum creatinine levels [88].

Infection is a usual trigger of HF hospitalization and it is related to increased mortality [89]. Patients with COVID-19 are not the exception [90]. The prevalence of coexisting HF ranged from 3.3 to 21% among SARS-CoV-2-infected patients, whereas during COVID-19 hospitalization, approximately one-third of patients with a history of HF had an acute decompensation of HF [85]. Cytokine storm in severe COVID-19 can increase metabolic demand and also provokes RAAS and sympathetic system activation which all entail high cardiac output and can lead to acute decompensation of chronic HF [91].

Critically ill COVID-19 patients are a specifically vulnerable group to developing acute renal injury. Except for the effect of nephrotoxic drugs on renal function, hemodynamic derangement and cytokine storm, kidneys are menaced by direct viral injury mediated by the abundant ACE2 receptors in their cells [92, 93]. Microthrombosis in renal vasculature also participate in renal dysfunction and acute renal injury in COVID-19 patients [94]. Up to 11% of hospitalized patients and 25% of critically ill patients is

estimated to be afflicted by acute kidney injury [95]. Loss of glomerular filtration rate accelerates the disease progression and predisposes to acute decompensations in patients with a history of HF [95].

3.4. COVID-19 AND ARRHYTHMIAS

Cardiac arrhythmias have been recognized as a frequent complication of COVID-19 infection. In a prospective observational study of 143 COVID-19 hospitalized patients followed with telemetry monitoring, sinus tachycardia afflicted 39.9% of patients, while premature ventricular contractions (PVCs) were observed in 28.7% and non-sustained ventricular tachycardia (VT) in 15.4% of patients (the mean follow-up was 23.7 days). The presence of sinus tachycardia was correlated with a less favorable outcome [96]. In a retrospective cohort of 241 patients hospitalized with COVID-19 the incidence of cardiac arrhythmias was 8.7%, whereas the presence of HF was associated with an increased hazard of new onset arrhythmia [97].

A prospective study including 113 SARS-COV-2 positive patients admitted to ICU, demonstrated a prevalence of sustained atrial arrhythmias in 44.2% of patients and a 33.6% of non-sustained atrial arrhythmias, with the most prevalent atrial arrhythmia being atrial fibrillation (AF) [98]. Ventricular arrhythmias were recorded in a total of 30.9% of patients; significantly higher than the prevalence of ventricular arrhythmias in non-COVID ICU patients reported in previous studies [99, 100]. Approximately, 1 out of 4 of the patients had at least one bradycardic episode. In 8.9% of this subgroup, AV conduction disorders was the observed episode with a third-degree AV block being the predominant subtype of AV conduction disorder [98].

During COVID-19 infection diverse mechanisms participate in the genesis of arrhythmias. SARS-COV-2 can engender arrhythmias through direct myocardial damage causing acute myocarditis or through HF decompensation or secondary, through respiratory failure or severe respiratory distress syndrome [101]. Direct viral myocardial injury to the conduction system can also predispose to arrhythmogenesis [42, 102]. Other possible mechanisms include drug side effects, electrolyte derangements, and autonomic or fluid imbalance.

3.4.1. Supraventricular arrhythmias

Atrial fibrillation/atrial flutter occur in approximately 15-20% of patients hospitalized with COVID-19 [103]. Factors like older age (senility) and obesity that make patients more susceptible to infection, also predispose to AF [104]. Hypoxemia and impaired gas exchange in patients with pneumonia increases the anaerobic fermentation and triggers imbalances in myocardial cells action potential promoting the development of AF [104, 105]. Stimulation of sympathetic nervous system may also contribute to AF development [105]. Macrophage infiltration, monocyte chemoattractant protein-1, interleukin-6, vascular endothelial growth factor, matrix metalloproteinase-2, tumor necrosis factor-α, and matrix metalloproteinase-9 are encountered in inflammatory state and have been positively related to AF and associated with atrial myocardial fibrosis [106]. Common drugs such as corticosteroids and aminophylline given in COVID-19 may have an effect on AF incidence [107]. QTc interval should be measured to avoid a marked prolongation in cases of co-administration of other QT-prolonging drugs [103, 108]. Intravenous (IV) amiodarone is the recommended antiarrhythmic drug for rate and rhythm control. However, its combination with hydroxychloroquine and/or azithromycin should be avoided in COVID-19 patients [103]. COVID-19 is associated with significant risk of venous, arterial, and microvascular thrombotic and thromboembolic disease. Therefore, special attention should be given to anticoagulation therapy administration, taking in mind that CHA2DS2-VASc score may underestimate risk of stroke [103, 109].

3.4.2. Ventricular arrhythmias

Patients with myocardial injury and myocarditis present a high burden of ventricular ectopy. In the setting of COVID-19 infection accompanied by myocardial damage, various ventricular arrhythmias can complicate the clinical course, increasing disease's mortality. Electrolyte disturbances due to volume depletion or acute kidney injury, affect an average of 7.2% of COVID-19 patients and also predispose to emergence of ventricular arrhythmias [110]. Non-sustained VT, multiple ventricular premature conductions, sustained VT and VF have all been encountered in COVID-19 patients [111]. In a single-center retrospective analysis the incidence of sustained VT or VF in

hospitalized COVID-19 patients was reported to be 5.9% [31]. Polypharmacy in fragile patients or in patients with comorbidities may be culpable of QT prolongation leading to the development of polymorphic VT. Special attention should be paid to COVID-19 therapies that present an increased risk for TdP due to QT prolongation [108]. Hydroxychloroquine/chloroquine and azithromycin prolong action potential and trigger early after depolarization which can stimulate TdP. In a meta-analysis of forty-seven studies including 13,087 COVID-19 patients the abovementioned treatment (hydroxychloroquine alone or in combination with azithromycin) lead to a significantly elevated prevalence of QTc prolongation [108]. . COVID-19-associated cytokine surge may trigger ventricular ectopy in previously clinically silent cardiomyopathies or patients with chronic coronary syndromes. A VT storm occurring in an afebrile and otherwise asymptomatic SARS-COV-2 positive patient has been reported, unmasking a previously unknown substrate of arrhythmogenic right ventricular cardiomyopathy (ARVC) [112].

3.4.3. Bradycardia and conduction abnormalities

In small case series, transient sinus bradycardia has been reported as a manifestation of the COVID-19 disease. Sinus bradycardia episodes were unrelated to previous cardiovascular history [113]. Bradycardia episodes are attributed to hypoxia and inflammatory damage of the cardiac pacemaker cells and indicate a cross-talk between the autonomic nervous system and immune system [114]. Interestingly, bradycardia slightly precede cytokine storm, denoting a timepoint of clinical deterioration [115]. Intermittent 3rd-degree AV block during hospitalization with COVID-19 has also been described.

Sinus bradycardia or AV block can be caused by drugs such as hydroxychloroquine, lopinavir/ rotinavir and azithromycin. Myocarditis affecting the sinus node can also be a cause of bradycardia [111]. Given the fact that bradycardia and atrioventricular conduction disorders in COVID-19 patients are mostly transient, the use of isoprenaline or implantation of a temporary pacemaker and subsequently evaluating the need of a permanent pacemaker, is a reasonable option [103, 109, 116].

3.5. COVID-19 AND STATIN THERAPY

The link between statin therapy and COVID-19 severity and outcomes is of intense interest at present. Several studies have demonstrated the association between statin therapy and reduced risk of pneumonia, milder disease, as well as reduced mortality [117-119] However, an Italian multicenter observational study, which enrolled 842 hospitalized patients with COVID-19, revealed no association between the use of statin and in-hospital mortality (P = 0.185). Interestingly, statin use was associated with a more severe disease (National Early Warning Score ≥5, P = 0.025), reflecting the presence of cardiovascular risk factors as dyslipidemia or coronary artery disease in those patients [120].

CONCLUSION

SARS-CoV-2, a single stranded RNA beta coronavirus, causes COVID-19 disease. The affinity of SAR-COV-2 infection to ACE-2 receptor has been proposed to be the core of the disease's pathophysiology. Although SARS-COV-2 infection predominantly offends the respiratory system, it is liable for various cardiovascular complications such as ACS, myocarditis, HF and arrhythmias. Several mechanisms have been implicated such as excessive inflammatory response to the primary infection, immunothrombosis, and myocardial injury (Figure 4). SARS-COV-2 infected patients with a history of cardiovascular disease have increased mortality.

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