Chapter

COVID-19 and Cardiovascular Disease: Mechanisms and Implications

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Abstract

We are living and fighting serious COVID-19 pandemic, which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. Cardiovascular diseases are highly prevalent in the infected individuals, which modifies their treatment and prognosis. The injury of the myocardium is reported in over 15% of hospitalized severely ill patients, mostly presented in the form of acute heart failure, acute coronary syndrome, cardiac arrythmias, myocarditis and thromboembolic complications. All these complications may appear at early in the course of the disease, during the disease progress or in the later stage of the COVID-19 disease. Thromboembolic complications accompany more severe cases, caused by excessive inflammation, platelet activation, endothelial dysfunction, and stasis. This new virus pandemic is a global challenge for health care system where we still have much to learn.

Keywords: COVID-19, pandemic, myocardial injury, cardiovascular disease

1. Introduction

The COVID-19 pandemic has opened up many serious challenges to the world. The pandemic has put enormous pressure on healthcare systems worldwide. There are many unknown puzzles the virus imposes to us as medical professionals. Most data we have come from China, Italy, France and USA and management is guided by the expert opinion. While COVID-19 primarily affects the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), it can also affect multiple organs, particularly cardiovascular system. Mortality and complications risk is increased by the presence of several comorbidities: cardiovascular disease, hypertension, diabetes, obesity, chronic pulmonary disease, and cancer [1]. Cardiovascular system in COVID-19 infection is affected in up to 15% of severely ill patients on multiple levels, which leads to increased morbidity but also it might induce myocardial injury leading to myocardial dysfunction [2]. The most common complications include arrhythmia (atrial fibrillation, ventricular tachyarrhythmia, and ventricular fibrillation), cardiac injury (elevated highly sensitive troponin I (hs-TnI) and creatine kinase (CK) levels, NT pro-BNP levels), fulminant myocarditis, heart failure, pulmonary embolism, and disseminated intravascular coagulation (DIC) [3].

Patients with established heart disease constitute a particularly challenging group, with conditions that may be life-threatening if proper treatment or intervention is inadequately delayed, which is the base for increased complications risk and

worsened disease prognosis. COVID-19 case fatality rate is significantly different around the world. Patients with several comorbidities have significantly increased case fatality rate (CFR): 10.5% for cardiovascular disease (CVD); 7.3% for diabetes mellitus; 6.3% for chronic obstructive pulmonary disease (COPD); around 6% for hypertension patients with cancer [4]. The mortality rates are different in different world regions and are influenced by several technical and quality measures of the healthcare systems, number of tests performed, demographic characteristics of the tested population and their health status. These aspects underline the importance of the need for multidisciplinary assessment and treatment, including cardiovascular evaluation and therapy aimed to reduce the COVID-19 mortality.

2. COVID-19 and cardiovascular system

Published data about disease manifestation and progression showed that patients with established cardiovascular disease are among the highest risk individuals for severe manifestation of COVID 19 and death. In a series of 44 672 confirmed patients with COVID-19 from China, 14.2% were reported to have cardiovascular disease, but also 22,7% of all deaths were in patients with underlying cardiovascular disease [5, 6]. The presence of common risk factors, such as hypertension, diabetes, coronary artery disease (CAD) increase the risk for COVID-19 induced complications as shown in **Figure 1**. It is of greater concern and importance the fact that COVID-19 can lead to cardiac injury even in individual not reporting previous cardiovascular disease. There is a need for proper understanding of the pathophysiological mechanisms of the cardiovascular damage caused by COVID-19 disease. This will enable on time effective patient's management and mortality reduction. The affection of the cardiovascular system by the infection is followed by release of inflammatory markers such as highly sensitive troponin and natriuretic peptides, which modifies prognosis, particularly in patients with continuous rise of those markers [7]. Cytokines such as IL-6 causes inflammation of the vascular system that result in generalized endotheliopathy and immune induced thrombosis. Inflammation in the myocardium can lead to myocarditis, heart failure, cardiac arrhythmias, and sudden death [7, 8]. Down-regulation of ACE2 with viral infection may predispose to relatively unopposed angiotensin II effects, which and cause new or worsened hypertension. After infection with common RNA viruses, most infected patients may experience only a transient viral syndrome with no significant cardiac dysfunction. However, depending on the immune response it can manifest as acute myocarditis with heart failure or cardiogenic shock, accompanied by cytokine storm and inflammatory cell infiltration of the heart. With proper treatment some patients can recover, but others can develop inflammatory cardiomyopathy [9].

A place of the initial *SARS-CoV-2* virus entrance to our organism is virus attachment to the angiotensin converting-enzyme 2 (ACE-2) membrane-linked aminopeptidase receptor on the epithelial cells of the lungs. However, these receptors are expressed in many human organs including myocardium making them vulnerable to the virus [10]. The studies showed higher expression of ACE-2 receptors in diabetic and hypertensive patients, which might be one of the causes of more severe forms of the disease in those individuals. While ACE2 is essential for viral invasion, there is no evidence that ACE inhibitors or angiotensin receptor blockers (ARBs) worsen prognosis. Hence, patients should not discontinue their use, based on recommendations for COVID-19 and cardiovascular disease treatment from several cardiology associations. Moreover, renin–angiotensin–aldosterone system (RAAS) inhibitors might be beneficial in COVID-19 [10]. Initial immune and inflammatory

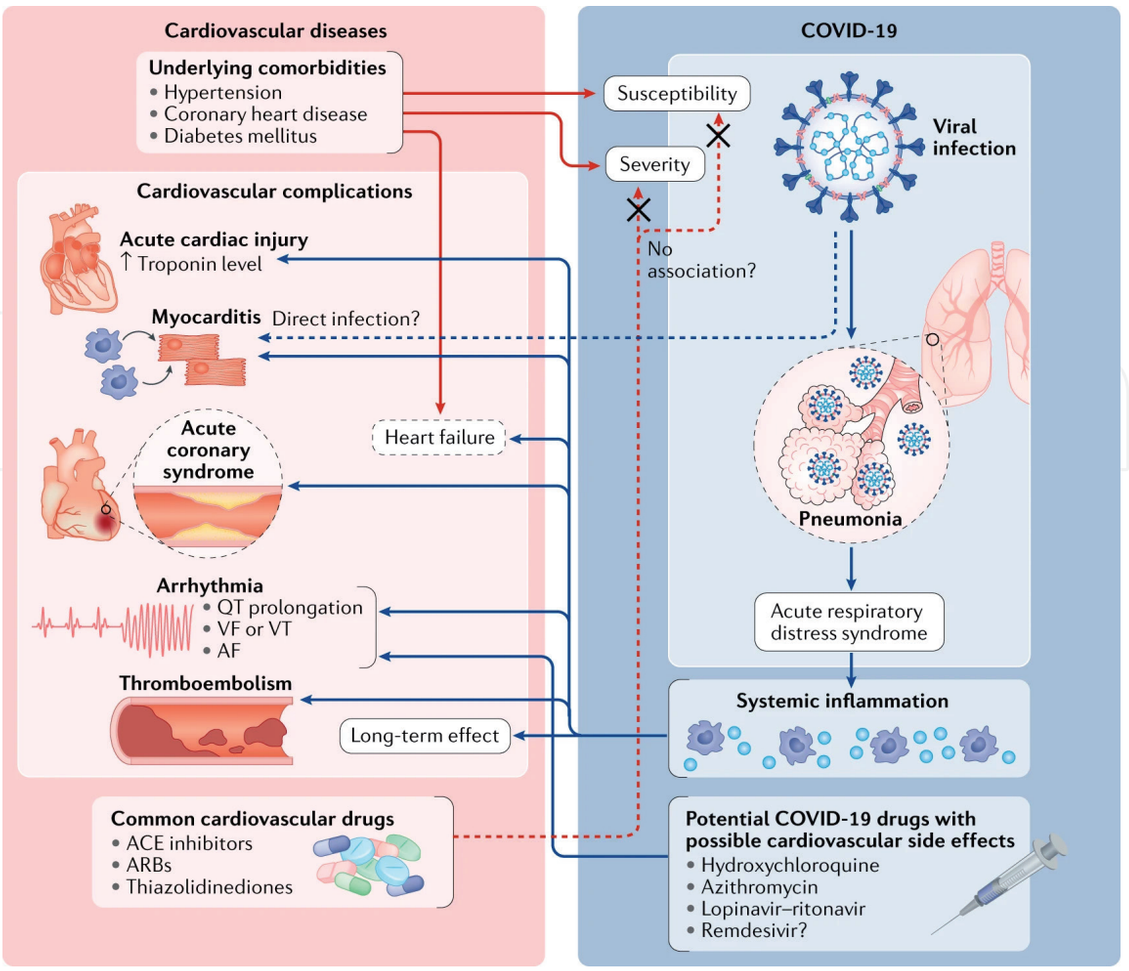

Figure 1.
In COVID-19 disease patients' cardiovascular comorbidities are the cause of the increased mortality. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) which are established drugs for reduction of the cardiovascular risk have many positive effects that might modify the course of the COVID-19 disease. Nature Reviews Cardiology volume 17, pages 543–558(2020), ref. [7].

responses induce a severe cytokine storm during the rapid progression phase of COVID-19. Early evaluation and continued monitoring of cardiac damage using the values of high sensitive cardiac troponin I (hs-cTn I), N-terminal *pro* b-type natriuretic peptide (NT-proBNP) and coagulation (D-dimer) after hospitalizationmay identify patients with cardiac injury and predict COVID-19 complications [11]. Severe inflammation is assumed as a cause of underlying generalized endothelial disfunction (endotheliopathy), which serves as a basis for development of microvascular thrombosis.

2.1 Cardiac injury caused by COVID-19 infection

The data from published studies showed that patients with myocardial injury (elevated cardiac troponin), have up to three times higher hospital mortality [12]. Increased hospital values of the high-sensitivity cardiac troponin I are found in over 50% of fatal COVID-19 disease cases. Elevation of the troponin values parallel the elevation of N-terminal pro-B-type natriuretic peptide and C-reactive protein and markers of cardiac injury and inflammation. Data showing the rise of the troponin in the same time with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase), lead to conclusion that isolated myocardial injury mediated through ACE-2 is not the only mechanism of COVID-19 induced

cardiac lesions [13]. One of the explanations is the presence of cytokine storm. The curves of troponin values changes show slow elevation during the first 2 weeks, with steep elevation during the third week in severely and critical ill patients with severe disease forms. Follow up studies showed that hs- Troponin I value in survivors have no significant changes [14].

Many patients' cases with of ST segment elevation myocardial infarctions (STEMI) with normal coronary angiography findings are published [15] which is explained as injury caused by stress cardiomyopathy or acute myocarditis. However, so far there are no published data of the signs of direct virus infiltration of the myocardium. The scientific data we have indicates inflammation as a cause of multi-organ damage, not only myocardial damage. Use of cardiac magnetic resonance imaging may give more answers to these questions.

There are evidences of impaired heart function due to myocardial injury in patients who recover from COVID-19, mostly due to myocarditis. Based on all data we have we can evaluate troponin levels as markers on disease severity and myocardial injury, also related to the underlying mechanisms such as cytokine storm, tissue hypoxia, and coagulation disturbances [16]. Management of the myocardial injury and their consequences are of great clinical and prognostic importance in critically ill individuals. We should not initially use invasive diagnostic procedures in patients with COVID-19 disease and isolated troponin elevation in absence of other signs and symptoms suggesting the presence of acute coronary syndrome.

2.2 Which biomarkers should we measure?

As in patients without COVID-19, cardiac troponin T and troponin I values should be measured based on clinical presentations when T1 type myocardial infarction (MI) is suspected [17]. Normal high -sensitive cardiac troponin values depend on gender and essay analyses used. Diagnostic algorithms for rapid rule out and/or rule-in of MI in patients with acute chest discomfort such as the high-sensitivity cardiac troponin (hs-cTn) T or I 0/1 hour algorithm is expected to provide comparable performance and add to diagnosis in other challenging subgroups with higher baseline concentrations such patients with renal dysfunction: very high safety for rule-out and high accuracy for rule-in, but reduced efficacy with a higher percentage of patients remaining in the observe zone [17, 18]. Clinical assessment including chest pain characteristics, hs-cTn T or I measurement at 3 hours, and cardiac imaging using echocardiography are the key elements for the identification of STEMI in the setting of COVID-19 infection. Hs-cTn I should be measured in patients with confirmed pulmonary embolism, as a marker for risk stratification and prognosis [19].

Similarly, B-type natriuretic peptide (BNP) and NT-proBNP should be measured whenever clinically heart failure is suspected [19]. Rule-in cut-offs for heart failure (HF) maintain high positive predictive value even in patients with pneumonia, who are not critically ill. Having in mind that most of the critical ill patients have significantly higher BNP/NT-proBNP values, it is therefore not recommended to use current cut-off values applied for heart failure patients. Increased BNP/NT-proBNP levels in severely ill patients with COVID-19 disease are explained by the presence of hemodynamic stress and myocardial injury leading to heart failure [20]. Cardiac injury, as assessed by several serum analysis parameters (lactate dehydrogenase, cardiac troponin I, creatine kinase (-MB) and myoglobin), were associated with poor prognosis in COVID-19 infection, assessed in. the retrospective multicenter study from Xie and coworkers, as shown in **Figure 2** [21].

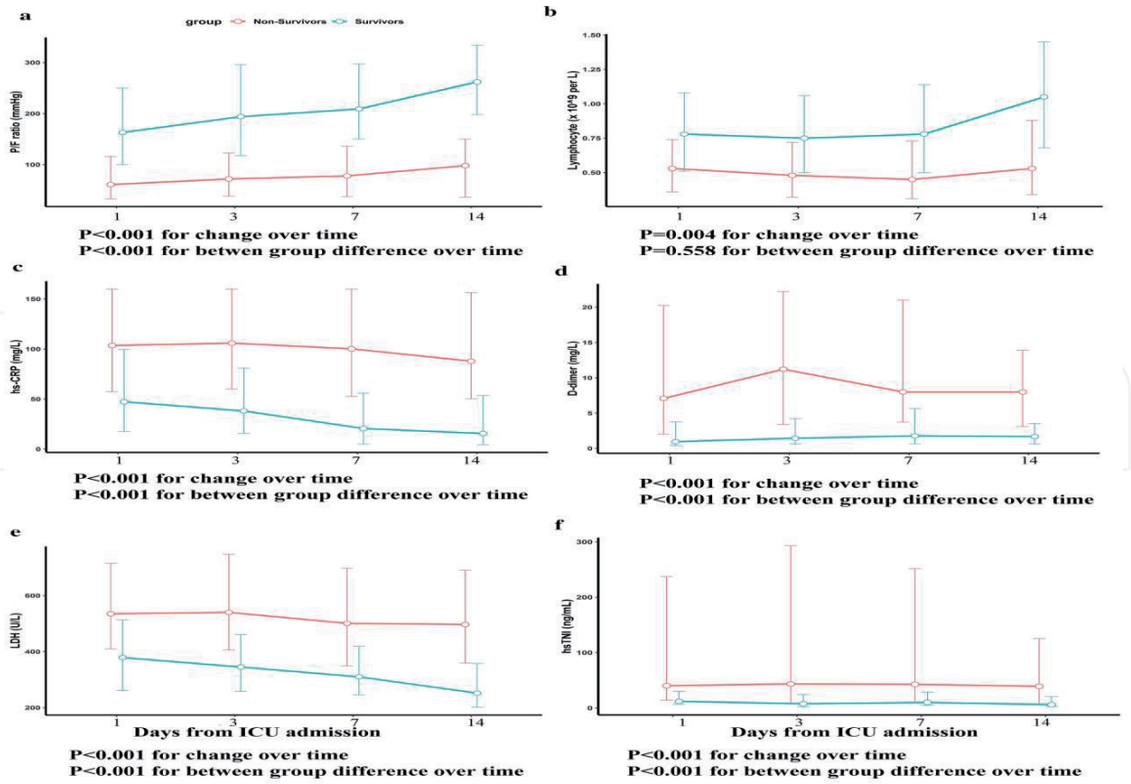

Figure 2.
Dynamic changes in laboratory markers of severely ill patients with COVID-19 disease hospitalized in the intensive care units (ICU). The figure describes changes in the arterial pO2 ("P") from the ABG divided by the FIO2 ("F") (P/F ratio) which includes the values of lymphocytes, high sensitive C reactive protein (hs-CRP), D-dimer, lactate dehydrogenase (LDH) and high sensitive troponin I (hs-troponin I) (a-f). At all-time points shown, there were significant differences between survivors and non-survivors. Intensive care medicine volume 46, pages1863–187, 2020 (ref [21].

2.3 COVID-19 and Heart failure

COVID-19 infection might present as new or worsened previously established heart failure. It is a challenge for every physician to make differential diagnoses between decompensated heart failure (HF), often complicated with pulmonary infection and COVID-19 infection, prior to laboratory-confirmation. There are significant similarities between chest computer tomography (CT) findings of the patients with heart failure and those with COVID-19 disease. Higher ratios of central ground glass opacity are found in patients with heart failure, comparing to the more peripheral gradient distribution in patients with COVID-19 infection [22].

Scientific data reports up to 25% of case fatality rate in patients with extreme elevation of NTproBNP levels caused by heart failure and cardiac arrest [23]. In a large cohort from China, heart failure was reported in 23% of infected patients and the prevalence was significantly higher among non-survivors (52% vs. 12%, $p < 0.0001$) [23].

From the evidences we have so far, patients with previous heart failure will have more complicated pulmonary disease and COVID-19 infection course. Acute heart failure and myocarditis might be one of the clinical presentations of COVID-19 disease. Some of the explanations of the underlying mechanisms of the heart dysfunction are initial structural changes in the early stage of the disease with preserved left ejection fraction in parallel with pulmonary complications and the development of acute heart failure with reduction of systolic function in the later stage of the disease as a response to cytokine storm.

Heart failure has been reported as an outcome in 23% of COVID subjects in a recent report from in-hospital Chinese subjects. Approximately 52% of

non-survivors had heart failure as compared with 12% of survivors [24, 25] Mechanisms underlying myocardial injury remain unknown and it is unclear whether they reflect systemic, local, ischemic or inflammatory process. It is still not known whether acute injury is a primary infective phenomenon or secondary to lung disease.

Elderly patients with heart failure may have left ventricular hypertrophy, diastolic dysfunction or systolic dysfunction and are prone to higher pulmonary vascular pressure in case of overload with fluid infusions and administration of parenteral therapy. Myocardial injury is observed in more than 20% of hospitalized patients with COVID-19 [26]. Increased levels of brain natriuretic peptide or N-terminal pro brain natriuretic peptide may be found in COVID-19 patients and may suggest concomitant impairment of cardiac function and poorer clinical course. Patients with elevated troponin levels have higher rates of major complications, including cardiac arrhythmias, acute kidney injury, ARDS, need for mechanical ventilation, and death [26].

Most patients with heart failure have elevated C-reactive protein, erythrocyte sedimentation rate and other indexes of inflammation and thrombogenicity, such as ferritin, interleukin-6, lactate dehydrogenase, fibrinogen, and D-dimer. An increase in these markersis associated with high mortality [27]. All these markers are higher with continuing increase during the hospitalization in high risk patients who do not survive the disease. Contrary in lower risk stable patients who survive all these parameters remains stable and relatively low. Procalcitonin must be measured when bacterial superinfection is suspected. Echocardiography must be considered in all patients with HF and suspected or confirmed COVID-19 infection to assess cardiac function and to detect concomitant causes of HF, either pre-existing or COVID-19-related (e.g. right ventricular dysfunction secondary to pulmonary embolism). Treatment of heart failure patients should be based on the latest guidelines from several cardiology societies [17, 28].

2.4 COVID-19 and Coronary artery disease

Patients with coronary artery disease, stabile or unstable, are prone to complications during COVID-19 infection, due to coronary plaque rupture or stent-thrombosis secondary to pro-coagulant effects of systemic inflammation [28]. Around 6% of patients with severe COVID-19 disease report the history of previous coronary artery disease (CAD), comparing with 1.8% prevalence of CAD in patients with non-severe disease forms [18].

It is important to underline that many individuals with COVID-19 disease initially presents with chest pain, palpitation and dyspnea instead of cough, fever and other related respiratory symptoms. Normal coronary angiography in patients presenting with chest pain and suspected acute coronary syndrome, should raise the first suspicion of infection with COVID-19. However, elevated troponin during COVID-19 infection, if followed by typical symptoms and signs of myocardial infarction should lead to guideline-directed interventions, fibrinolysis, or coronary angioplasty in designated hospitals [18, 28]. There are evidences of high expression of angiotensin II receptors in the heart muscle [29]. These findings explain the SARS-CoV-2 infection repercussion on the myocardium in the form of locally induced microvascular inflammation and dysfunction leading to myocardial infarction without the obstruction of the coronary arteries (MINOCA). All these pathophysiological mechanisms could explain the scientific data we have obtained concerning the clinical course of patients presenting with myocardial infarction signs during the COVID-19 disease [30]. Additionally, cytokine storm significantly contributes for the development of the endotheliopathy through well described mechanisms. The global finding during

the COVID-19 pandemic is significant reduction of number of acute myocardial infarction by 30–50%, mostly due to fear for on time search of medical help [31]. The late patient's presentation leads to significant increase of acute myocardial infarction complications, especially heart failure.

Several pathways associated with viral diseases may contribute to destabilize plaques in COVID-19 patients [32]. Viral illness can potentially destabilize atherosclerotic plaques through systemic inflammatory responses, cytokine storm, as well as specific changes of immune cell polarization towards more unstable phenotypes. In patients with viral infections, type 2 myocardial infarction is the most common subtype, were the usefulness of invasive treatment with coronary revascularization is limited.

In patients with acute coronary syndrome (ACS) and COVID-19 disease the final treatment decision weather invasive or medical management is applied should be carefully considered. Primary percutaneous coronary intervention (PCI) is the standard treatment for patients presenting to PCI centers within 90 minutes of first medical contact [28, 33]. It is important to underline that all patients presenting with a suspected STEMI should be considered COVID-19 possible. Testing for SARS-CoV-2 should be performed as soon as possible following first medical contact, irrespective of treatment strategy, in order to allow to implement adequate protective measures and management pathways [28]. Some of these patients may have a "STEMI-mimicker" such as focal myocarditis or stress cardiomyopathy known to be associated with COVID-19 illness.

Treatment of patients with non-ST segment elevation myocardial infarction non-STEMI should be guided by risk stratification. Patients with Troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach. For patients at high risk, medical strategy aims at stabilization whilst planning an early (< 24 hours) invasive strategy.

The use of timely reperfusion in STEMI patients should not be compromised by the COVID-19 pandemic. Based on the recommendations from the latest guidelines of the European Society of Cardiology (ESC), reperfusion therapy is indicated in STEMI patients with ischemia symptoms in duration <12 hours and persistent ST segment elevation in at least 2 ECG leads, and these recommendations remain the same for COVID -19 disease patients with STEMI. The maximum delay from STEMI diagnosis to reperfusion of 120 minutes should remain the goal for reperfusion therapy with primary PCI when feasible within this time frame and performed in facilities approved for the treatment of COVID-19 patients [28]. If primary PCI performing hospital is no not available or target time cannot be met and fibrinolysis is not contraindicated, fibrinolysis should then become first line therapy [28, 34].

2.5 COVID-19 and myocarditis

Injury of the myocardium and acute myocardial inflammation are well documented complications of acute viral infections. One of the underlying mechanisms of the injury, obtained from the cardiac muscle autopsy specimens are myocytes necrosis with mononuclear cell infiltrates [35]. These findings together with the cases of fulminant myocarditis, lead as to conclude that myocarditis is an important cause of acute myocardial injury in patients with COVID-19 disease. However, the true prevalence, the exact mechanisms and clinical significance of acute myocarditis in COVID-19 patients still remains unclear. We do not have solid evidence of direct myocardial cytotoxic effects of the virus. The real prevalence of this complication still remains unclear. Myocarditis appears in COVID-19 patients after a prolonged period up to two weeks after the symptom's onset.

Clinically, COVID-19 myocarditis may manifest only as mild chest discomfort, palpitation and fatigue, which may be impossible to distinguish from other causes in most patients. In some patients, myocarditis results in fulminant disease, which may be the cause of arrhythmias, conduction block, myocardial dysfunction or even death. In many cases myocarditis is suspected when cardiac injury is present in the absence of ACS [36]. Acute myocarditis diagnosis can be confirmed by the presence of typical acute myocardial injury signals detected by cardiac magnetic resonance imaging (MRI). However Cardiac MRI and EMBs as diagnostic tools are likely to be inappropriate during the current COVID-19 pandemic but should be considered in the later phase to confirm diagnosis.

This cardiac injury in COVID 19 infected patients leads to activation of the innate immune response with release of proinflammatory cytokines. Proteins released through cell lysis might display epitopes similar to the viral antigens and be presented via the major histocompatibility complex [37]. An acquired immune response is the predominant mechanism evidenced by activation of antibodies and T lymphocytes. In the final stage, there is either recovery or low levels of chronic inflammation with concomitant development of left ventricular dysfunction. The most important question for potential therapeutic targets is the extent to which myocardial injury results from viral replication, is immune mediated, or is due to other mechanisms. Patients that develop heart failure have poor prognosis and should be treated based on heart failure guidelines [28]. Clinical follow up, with biomarkers and echocardiography are important for patient's treatment and prognosis [38].

2.6 Arrhythmias and sudden cardiac death

In-hospital and out-of-hospital sudden cardiac arrests have also been reported in patients with COVID-19 [39]. The contribution of COVID-19 disease for induction of cardiac arrhythmias remains uncertain, having in mind that atrial and ventricular arrhythmias can also be triggered by myocardial injury, other infections, fever, sepsis, hypoxia and electrolyte abnormalities. Arrhythmias can be induced by concomitant antiviral and antibiotic therapy used in patients with COVID-19 disease. Increase heart rate is reported as one of the main symptom in COVID-19 disease patients without other symptoms such as fever or caught. The presence of cardiac arrhythmias was reported in 17% of patient from the cohort of 138 COVID-19 cases in the study from Wuhan, China, and 44% of them were hospitalized in the ICU units [39]. Another study from Wuhan which includes 187 hospitalized COVDI-19 patients, showed that patients with elevated troponin T values were more likely to develop serious arrhythmias, including ventricular tachycardia and fibrillation, comparing to those with normal troponin T levels (12% vs. 5%) [40]. Treatment of all systemic causes and underlying heart injury having in mind drug interactions should remain the arrhythmias management goals in COVID 19 patients [28]. Hospital data from China revealed that hospitalized COVID-19 patients with elevated troponin levels had more frequent malignant arrhythmias (11.5% vs. 5.2%) and higher overall mortality (59.6% vs. 8.9%) [41].

2.7 COVID-19 and coagulation abnormalities

Thromboembolic complications are highly prevalent in patients with COVID-19 infection. Disseminated intravascular coagulation (DIC) and pulmonary embolism, characterized by increased D-dimer levels and fibrin degradation products, are the most characteristic clinical presentations. DIC has been observed in 71.4% of non-survivors [42]. Pulmonary embolism (PE) has been reported in up to 30% of hospitalized patients [41, 43]. Those percentages might not be surprising given the

critical condition of these subjects. The clinical and scientific data we have from several world centers indicates that D-dimer values are highly predictive of adverse events in patients with COVID-19 disease. Results from retrospective cohort study showed that elevated D-dimer values (>1 g/L) are strongly associated with intrahospital mortality, which was confirmed as a relationship in the multivariate analysis (OR 18.4, 95% CI 2.6–128.6; p = 0.003) [44]. Additionally, Chinese and Italian experience emphasizes that in the earlier stage of the disease more discrete D-dimer changes are observed, which precede the rapid rise of D-dimer as disease progresses. Recommended diagnostic algorithms combing pre-test probability assessment and D dimer tests can be used in case of suspected acute PE.

Hypercoagulability caused by inflammation and cytokine release are the underlying cause for pulmonary embolism in COVID-19 infected patients [45]. Advanced age, bedridden, stasis, endothelial injury and hemostatic abnormalities are factors associated with increased risk for venous thromboembolism. Inflammatory activation in COVID-19 leads to frequent abnormalities in the coagulation system [45]. It is assumed that COVID -19 infection lead to generalized endotheliopathy as a one of the underlying mechanisms for impaired vascular function and hypercoagulability. For risk stratification purposes and prognosis as well as identification of the patients with increased thrombotic risk, markers of inflammation and thrombotic risk should be measured at baseline and repeated every 2–3 days if abnormal and whenever clinical deterioration is suspected.

The index of suspicion for VTE should be high in the case of typical deep vein thrombosis (DVT) symptoms, hypoxemia disproportionate to known respiratory pathologies, acute unexplained right ventricular dysfunction, new or unexplained tachycardia and new onset of ECG changes suggestive of PE, fall in blood pressure not attributable to tachyarrhythmia, hypovolemia or sepsis [46].

A diagnostic challenge arises among patients with COVID-19, as imaging studies used to diagnose DVT or PE may not be performed given risk of transmitting infection to other patients or health care workers and potentially due to patient instability. Prophylactic anticoagulation is recommended in all patients admitted with COVID-19 infection. When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current European Society of Cardiology (ESC) guidelines [28]. The novel oral non-vitamin K antagonists (NOACs) may show some interactions with the some of the drugs used in COVID-19 disease patients, mainly with lopinavir/ritonavir and in those cases NOACs should be avoided. There are no major interactions reported between investigational drugs for COVID-19 and the use of heparin as anticoagulant therapy [47].

3. Treatment in the light of cardiovascular disease

Regarding the treatment of the COVID-19 infection there are many trials from the beginning of April 2020. Based on the evidence we have so far, the treatment depends on clinical presentation, laboratory and imaging findings as indicated. Supportive care, starting from symptomatic measures, up to complete intensive care support is recommended [48].

There is a need of more research concerning the relationship between rennin-angiotensin-aldosterone blockade and COVID-19 disease in patients with cardiovascular conditions. From the recommendations and guidelines of the major cardiology societies we have so far, therapy with ACE inhibitors or angiotensin receptor blockators for other indications should not be discontinued [28, 49]. The evidences we have do not indicate increased risk of infection or worse clinical course in patient treated with these medications. From other side we have strong warnings

that discontinuation of the therapy with these drugs, which modifies prognosis in patients with cardiovascular disease, may increase cardiovascular mortality rates [50]. In heart failure patients the use of drugs that may alter salt and water balance and cause excessive fluid accumulation, such as non-steroid anti-inflammatory drugs (NSAID) should be avoided. Advanced heart failure should be treated and monitored by cardiologists, based on the latest guidelines for the management of heart failure [28].

In patients with COVID-19 disease and established CAD the use of drugs that stabilize plaques and modifies prognosis (statins, aspirin, beta blockers, ACE inhibitors) should be used as indicated in the current guidelines [51, 52]. We should minimize or avoid the use of diagnostic tests that are unnecessary and will not change the diagnostic and treatment decisions. Unnecessary diagnostic tests should be minimized, or in some cases avoided. These tests should be used in circumstances in which they could add to the management of patients with COVID-19. Prophylactic anticoagulation should be applied in all hospitalized patients with COVID-19 infection. Patients with acute confirmed PE should be treated based on risk stratification as recommended in the latest European Society of Cardiology (ESC) guidelines and National PERT Consortium [28, 46, 47].

3.1 Knowledge gaps and future directions

COVID-19 has emerged as a new disease almost one year ago and it is still impossible to discuss long-term outcome in patients recovering from infection. Impaired heart function due to myocardial damage in acute phase leads to poor prognosis in these patients. Follow up studies and more data are needed to make conclusions.

There are still many challenges, undiscovered mechanisms, pathobiology, clinical characteristics and prognostic markers of the COVID -19 disease which are continuously studied. Early signs and markers of myocardial injury and presence of new or worsened heart failure are bad prognostic parameters. Long term COVID-19 syndrome and post COVID cardiovascular repercussions are another field of ongoing and future research. Special attention should be taken on timely diagnosis, management and follow up of the cardiovascular complications of COVID-19 disease.

The current evidence of association between renin-angiotensin-aldosterone medications and ACE-2 levels with clinical outcome in COVID-19 infection is insufficient. More information needs to be generated.

4. Conclusion

Preexisting cardiovascular disease are common in patients with COVID-19 and those patients are at higher risk of morbidity and mortality. Myocardial injury is present in more than a 15% of severely ill patients. The interaction between the virus S protein and ACE 2 is believed to have important role in disease pathogenesis, especially in cardiovascular manifestations, that could be potential target for the prevention and treatment of COVID-19 infection. The continuation of clinically indicated ACEi or ARB therapy is recommended by many heart associations, based on the currently available evidence. Reduced physical activity due to lockdown measures also contribute to worsened control of cardiovascular risk factors. Having in mind the prevalence of cardiovascular complications our main strategy to fight the pandemic remains social distancing, personal protection, vaccination and regular therapy for all cardiovascular disease patients.

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References

[1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;doi: 10.1001/jama.2020.2648

[2] Zheng Y-Y, Ma Y-T, Zhang J-Y and Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. March 5, 2020. doi: 10.1038/s41569-020-0360-5

[3] Zhou P, Yang XL, Wang XG et.al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270-273

[4] Zhou F., Yu T., Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020

[5] Huayan X, Keke H, Rong X et al. Clinical Characteristics and Risk Factors of Cardiac Involvement in COVID-19. J Am Heart Assoc 2020 Sep 15;9(18)

[6] Zhonghua L, Xing B, Xue Z. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019

[7] Masataka N, Dao WW, Yaling H, David Bl, Joseph CW. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020 Sep;17(9):543-558

[8] Shi S, Qin M, Shen B, et al. Association of cardiac Injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020

[9] Xiong T.Y., Redwood S., Prendergast B., Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020

[10] Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11:875-79

[11] Juan-Juan Q , Xu C , Feng Z et al. Redefining Cardiac Biomarkers in Predicting Mortality of Inpatients With COVID-19. Hypertension 2020 Oct;76(4):1104-1112

[12] Michael B, Norbert F, Evangelos G, Karen S,and Andreas M. Zeiher Coronavirus Disease 2019 (COVID-19) and its implications for cardiovascular care: expert document from the German Cardiac Society and the World Heart Federation. Clin Res Cardiol. 2020 May 27: 1-14

[13] Tomasz JG, Saidi AM, Anthony D et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020 Aug 1; 116(10): 1666-1687

[14] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; doi: 10.1001/jamacardio.2020.0950

[15] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19) JAMA Cardiol. 2020 doi: 10.1001/jamacardio.2020.1017

[16] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020 doi: 10.1001/jamacardio.2020.0950

[17] Sarju G, Sourbha SD, Sachin S. Management of Cardiovascular Disease During Coronavirus Disease (COVID-19) Pandemic. Trends Cardiovasc Med. 2020 Aug; 30(6): 315-325

[18] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan. China: a retrospective cohort study. Lancet. 2020 28 March-3 April; 395(10229): 1054-1062

[19] Peter AK, Ola H, Andrew W, Stephen WS, Fred SA. Cardiac Troponin Testing in Patients with COVID-19: A Strategy for Testing and Reporting Results. *Clinical Chemistry*, hvaa225, https://doi.org/10.1093/clinchem/hvaa225

[20] He XW, Lai JS, Cheng J, et al. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients]. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48(0):E011

[21] Jianfeng Xe, Wenjuan W, Shusheng L, et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease (COVID-19) in China: a retrospective multicenter study. Intensive Care Med (2020) 46:1863-1872

[22] Kai-Cai L, Ping X Wei-Fu L, et al. CT manifestations of coronavirus disease-2019: A retrospective analysis of 73 cases by disease severity. European Journal of Radiology 126 (2020) 108941

[23] Mehra MR, Ruschitzka F, COVID-19 Illness and Heart Failure: A Missing Link? JACC: Heart Failure (2020), doi: https://doi.org/10.1016/j.jchf.2020.03.004

[24] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020

[25] Fei Zhou , Ting Yu , Ronghui Du. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 2020 Mar 28;395(10229):1054-1062

[26] Kensuke M, Benjamin M, Laurence J, Patrick O, and Olivier M. Impact of COVID-19 on the Cardiovascular System: A Review. J Clin Med. 2020 May; (5): 1407

[27] Muhammed K, Raveena KK, Kiran PZ and Amer H. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci. 2020 Aug 1; 254: 117788

[28] ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

[29] Liang C, Xiangjie L, Mingquan CYi F, and Chenglong X. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020 Mar 30: cvaa078. doi: 10.1093/cvr/cvaa078

[30] Francesca G, Kyriazoula Ch, Annamaria M et al. Acute Myocardial Infarction in the Time of COVID-19: A Review of Biological, Environmental, and Psychosocial Contributors. Int J Environ Res Public Health, 2020 Oct 9;17(20):7371.

[31] Jules M, Yves C, Pierre C, et al. Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patient profile in France: a registry study. Lancet Public Health. 2020 Oct;5(10):e536-e542.

[32] Oren O, Kopecky SL, Gluckman TJ et al. Coronavirus Disease 2019 (COVID-19): Epidemiology, Clinical Spectrum and Implications for the Cardiovascular Clinician. Available at:-https://www.acc.org/latest-in-cardiology/

articles/2020/04/06/11/08/covid-19-epidemiology-clinical-spectrum-and-implications-for-the-cv-clinician[Accessed 10 April 2020]

[33] Panayotis KV, Anastasios T, Ioannis K. Concerns for management of STEMI patients in the COVID-19 era: a paradox phenomenon. J Thromb Thrombolysis. 2020 Jul 30: 1-5

[34] Sukhjinder SN, Ricardo P, Sayan S. Optimal management of acute coronary syndromes in the era of COVID-19. Heart. 2020 Oct; 106(20): 1609-1616

[35] Xin-xin W, Chen Sh, Xiao-jie Huang, Lin S, Ling-jia Meng, Hui Liu, Shi-jie Zhang, Hong-jun Li, Fu-dong Lv. Histopathological features of multiorgan percutaneous tissue core biopsy in patients with COVID-19. J Clin Pathol 2020 Aug 26; jclinpath-2020-206623

[36] Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet. 2020;395(10235):1516

[37] Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, et al. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020;heartjnl-2020-317186. doi: 10.1136/heartjnl-2020-317186

[38] Bhurint S, Saman N, Daniele M et al. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020 Sep; 17(9): 1463-1471

[39] Rakesh Y. COVID-19 and sudden cardiac death: A new potential risk. Indian Heart J. 2020 Sep-Oct; 72(5): 333-336

[40] Mohit KT, Daniel M, Martin EG al. Malignant Arrhythmias in Patients With COVID-19. Incidence, Mechanisms, and Outcomes. Circulation: Arrhythmia and Electrophysiology. 2020 Nov; 13(11): e008920

[41] Guo T., Fan Y., Chen M. Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19) JAMA Cardiol. 2020;5(7):811-818

[42] David L. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020 Apr; 18(4): 786-787

[43] Yasser S, Manuela G, Marc L et al. Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. Ann Intensive Care. 2020; 10: 124

[44] Yumeng Yao, Jiatian Cao, Qingqing Wang, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020; 8: 49

[45] Mouhamed Yazan Abou-Ismail, Akiva Diamond, Sargam Kapoor. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020 Oct; 194: 101-115

[46] Rachel P. Rosovsky, Charles Grodzin, Richard Channick. Diagnosis and Treatment of Pulmonary Embolism During the Coronavirus Disease 2019 Pandemic A Position Paper From the National PERT Consortium: Chest. 2020 Aug 27, doi: 10.1016/j.chest.2020.08.2064

[47] Stavros V K, Guy M, Cecilia B et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *European Heart Journal*, Volume 41, Issue 4, 21 January 2020, Pages 543-603

[48] Maria N, Niamh O, Catrin Sohrabi, Mehdi Khan, Maliha Agha, and Riaz Agha. Evidence based management guideline for the COVID-19 pandemic - Review article. Int J Surg. 2020 May; 77: 206-216

[49] Lopes RD, Macedo AVS, de Barros e Silva PGM, Moll-Bernardes RJ et al. BRACE CORONA Investigators. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–The BRACE CORONA Trial. Am Heart J 2020;226:49-59

[50] Devan K, Katherine M, and Kathryn V. Update Alert: Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults. Ann Intern Med. 2020 Jun 25: L20-0887

[51] Sarju G, Sourbha SD, Sachin S et al. Management of Cardiovascular Disease During Coronavirus Disease (COVID-19) Pandemic. Trends Cardiovasc Med. 2020 Aug; 30(6): 315-325

[52] Charan Y, Brian CC, Brian J. Forrestal et al. Treatment of ST-Segment Elevation Myocardial Infarction During COVID-19 Pandemic. Cardiovasc Revasc Med. 2020 Aug; 21(8): 1024-1029