



Principal cardiovascular manifestations related to COVID-19

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Summary:

The global pandemic caused by COVID 19 is known for its respiratory target by causing the “Acute Respiratory Distress Syndrome”. However, the damage of SARS-Cov-2 affects the cardiovascular system also. In patients with COVID 19 without cardiac arrest history, the virus is implicated in the occurrence of several pathologies, which the most common are myocardial lesions, myocarditis, arrhythmia, heart failure, chronic coronary syndrome, and venous thromboembolic diseases. The situation is even more complicated in subjects with cardiovascular comorbidity because cardiovascular disease can worsen the prognosis. Also, COVID 19 therapy appears to be a heart threat because of its cardiovascular side effects. The objective of this work is to review the most common cardiac manifestations associated with COVID-19, based on data published to date, to understand the impact of this epidemic on the cardiovascular system.

Keywords : COVID-19, cardiovascular disease, cardiac manifestations.

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Introduction

The "Severe Acute Respiratory Syndrome" or "SARS-CoV-2" is the name given by WHO to the new coronavirus, first introduced in China in late 2019, causing respiratory distress syndrome called CORONA VIRUS DISEASE or (COVID-19) (1). The first case of infection was recorded in the Chinese city of Wuhan in Hubei, which is reported to be rapidly spread worldwide due to the lack of effective therapy and disease control guidelines, in addition to the increased rate of transmission of the virus «Ro between 2 and 3" (2). On 11 March 2020, WHO declared COVID-19 as a global pandemic, which has endangered health and the economy internationally (3). Up to 27 October 2020, the number of people with Covid-19 is estimated at more than 45 million people in more than 200 countries around the world, and whose deaths have exceeded 1.200,000 deaths (4). Indeed, the known target of SARS-CoV-2 is the respiratory system. However, some people with COVID -19 have had severe heart attacks (5). The increasing number of cases succumbing to severe and even fatal cardiovascular impacts has attracted the attention of researchers to start studies in this direction.

The cardiovascular damage caused by SARS-VOC-2 can manifest itself in two directions. On the one hand, the virus can cause heart damage that has no prior cardiovascular comorbidity. On the other hand, if COVID-19 infection occurs in a subject predisposing to cardiovascular disease, complications are more severe or even fatal (1,6). Also, therapy against COVID-19, which is still under investigation, presents a real concern because of its adverse effects on the cardiovascular system (7).

At the time of writing, no one can predict if the consequences of this pandemic have reached their full extent. The objective of our research is to review the main interactions between COVID-19 and cardiovascular diseases that pre-exist or caused by the new coronavirus infection, based on the work published to date, with a view to giving more specificity to the care provided to this more vulnerable category.

SARS-Cov-19: Properties and mechanism's action

- *Family: Coronaviridae*
- *RNA virus: the assembly of almost 31 nucleotides (the largest viral RNA).*
- *Case hood rate: about 3.8%*
- *Incubation: 1 to 14 days*

Scientific studies on coronaviruses are started since the previous epidemic of 2002-2004. It has shown their increased virulence due to their adaptive capacity in binding to human cells which facilitates the epidemic spread (8). Indeed, during the viral multiplication process, the virus's polymerase RNA has several replication errors that optimize mutations and recombination (9). In other words, coronavirus is both the result of the absence of the RNA polymerase error-correcting activity, responsible of the genetic replication, and of a high recombination frequency (10). In vitro, the only modification of an amino acid in the S protein aminoterminal region, has allowed to modify the tropism in a pig coronavirus which, from gastroenteric and respiratory, has become exclusively respiratory (8,11). This genetic variability has in the past been the cause of a change in tropism of a pig and avian s, coronavirus train and recently SARS-Cov-2 (10,12).

SARS-CoV2 owes its creation to a mutation that occurred by the insertion of a cleavage site at the junction of the S1-S2 sub-units at the virus attachment domain (spike protein), to its tissue receptor, which is the conversion enzyme of angiotensin ACE (13).

The angiotensin II conversion enzyme (ACE2) is a carboxypeptidase that is expressed by cells in different organs of body including, among others, the heart (14),, and his role is to negatively regulate the renin-angiotensin-aldosterone (RAA) system. It has a vasoconstrictor, pro-fibrosing and, pro-inflammatory effect and stimulates the aldosterone secretion by his fixation on the AT1 receptor (15). ACE2 converts angiotensin II into angiotensin [1-7], which has a vasodilator, anti-fibrosing and anti-inflammatory effect by attaching to its Mas receptor (2,16).

Based on some in vitro studies, there appears to be a positive correlation between the risk of COVID 19 infection and the level of ACE2 expression (17). Indeed, the fixation of the virus on ACE2 leads to a decrease in its activity, which is therefore considered as an aggravating factor for inflammatory lesions (18).

Severe clinical manifestations of COVID-19 are generally related to rapid viral replication, and also massive tissue infiltration of inflammatory cells accompanied by an excessive release of cytokines responsible for the cytokin storm which result an Acute Respiratory Distress Syndrome (EDS) (19).

Covid19, pre-existing cardiovascular risk factors and CVD

In COVID 19, patients with cardiovascular disease have more increased risk of developing a complicated form (20). Several factors such as HTA, age, diabetes, and dyslipidemia weaken the immune system, so their infection with COVID 19 only exacerbates this weakening, and thus predisposes patients to a more intense risk of cardiovascular events (21).

At the beginning of the epidemic, a cohort of 201 Covid19 patients in a Chinese study assumed that there was a link between morbi-mortality due to COVID19 and HTA (15,22). The risk of mortality was 1.7, and 1.82 were suffering from Acute Respiratory Distress Syndrome (EDS). Similarly, in a cohort of 191 patients, the risk of mortality was 3.05. According to the latest published mortality data, 35% of patients with COVID19 had a history of high blood pressure and 17% had a history of coronary heart disease (23). However, it should be noted that this proportion is higher in the most severe forms of COVID-19, with a prevalence of 50.3% for high blood pressure, 22.2% for diabetes, 25% for heart disease, and 16.7% for cerebrovascular disease (7). Early results of autopsies in Germany show that the most affected people suffer from prior cardiovascular disease, and that the virus could act directly on the blood vessels attached to ACE2, which is strongly expressed in the myocardium as its membrane receptor, destroying their endothelium which plays a major role in protection process and enusing blood from the various organs (5).

In general, CK-MB, LDH, NT-pro-BNP and hs-cTnI biomarkers are usually used in cardiology, whose high frequency is a sign of a heart injury (2). In the COVID 19 infection, an abnormally high concentrations of these biomarkers are recorded in patients with or without a history of cardiac disease. In China, between the first reported deaths, the markers of myocardial lesions were up to 20 times higher than normal. Also, a myocardial lesion can be practically experienced by high levels of troponin T, which was estimated at 35.3% in Chinese patients, including 144 patients (77%) survived and 43 patients died (23%) (24.2). This diagnosis suggests a strong link between the elevation of myocardial biomarkers and the severity of the disease and prognosis (2). In hospitalized patients, periodic verification of troponin and natriuretic peptide levels can target patients at increased risk of left ventricular dysfunction or arrhythmia (24).

In the chronic coronary syndrome (CCS) case, COVID 19 infection is synonymous with a negative prognosis. In Wuhan, there was a high mortality rate in COVID 19 patients

who had already suffered from CSC due to a decrease in cardiac functional reserve due to cardiac ischemia or necrosis in this category, causing sudden deterioration in the health of the infected person (25).

Another challenge in the fight against COVID 19 in patients with cardiovascular comorbidity is these cardiac complications that occurred because of antiviral or immunomodulator-based therapies. Between all the molecules used in COVID 19 therapy, the most controversial is hydroxychloroquine, because of its effects on QT elongation. This situation requires a follow-up of cardiac ultrasound depending on the envisaged therapy (2)

Cardiovascular events associated with COVID-19:

The virus is characterized by an incubation period between 1 and 14 days before the first clinical signs appear. The data available today indicate common clinical manifestations between infected people. The first signs of the disease were retained from a first set of Chinese patients consisting of 41 patients (26), whose most common symptoms are: fever (98%), cough (76%), weakness (44%), expectorations (28%), headache (8%), hemoptysis (5%), diarrhea (3%) (27). In some cases, the condition may develop into severe pneumonia (up to 15% of infected patients), acute respiratory distress syndrome, and multi-systemic failure (28).

At the cardiovascular level, the symptoms caused by COVID-19 mainly result in cardiac chest pain, accelerated palpitations (in 20-40% of hospitalized patients according to medRxiv and bioRxiv reports (29).

Recent publications on the most common cardiovascular comorbidities associated with COVID 19 focus on the presence of high blood pressure (35%), and coronary heart disease (17%) for mild cases of infection. In cases of more severe COVID 19 outbreaks, the prevalence was 50.3% for high blood pressure, 25% for heart disease, 22.2% for diabetes, and 16.7% for cerebrovascular disease. Age is a risk factor for covid19 patients, the mortality rate becomes higher from age 60 compared to the younger subject (30). The prevalence of CVD reported in different studies around the world is not widespread across all infected cases (1-14%). It only concerns cardiac complications found in hospitalized patients (4).

Acute myocardial lesions

Some cases of acute distress pneumonia, or hypoxelish lung disease due to COVID 19, are responsible for acute myocarditis lesions recognized by a drop or rise of troponin (2). In COVID 19 patients, high troponin levels are always associated with a severe complication and eventually result a pejorative prognosis (31).

The rise in troponin levels is an indication of myocardial lesions. In Wuhan, the diagnosis of the first 41 patients shows that 5 of them had a troponin level greater than 28pg/MI (32). In another sample of 68 fatal cases of COVID19, 5 people died of a circulatory disorder due to myocardial lesions or 7%, 36 patients died of respiratory failure or 53% and 22 patients died as a result of respiratory failure accompanied by myocardial lesions or 33%. Recent studies report that 7.2% to 17% of hospitalized patients suffer from acute myocardial lesions. (26.)

The mechanisms of cardiac damage are still poorly understood. It is not clear whether this is a primary infectious phenomenon or a secondary injury due to a prior lung infection caused by the virus (33). To date, there are no detailed studies to show a causal link between Covid19 infection and myocardial lesions (29, 34). However, this elevation is insufficient to confirm the presence of an acute myocardial lesion. Further tests such as an electrocardiogram or imaging are required to make a full judgment on the patient's condition (1).

Myocarditis

In a recent report published by the National Health Commission in China. autopsy results conducted on a myocardial sample of patients who died by covid19, proves the presence of myocardial inflammatory infiltrates associated with non-ischemic necrosis called myocarditis (35).

The virus's access to cardiomyocytes through specific receptors cause either cellular necrosis or apoptosis by activating his signaling mechanisms. In patients with covid19 myocarditis appears after 15 days of onset of symptoms (36). In a cohort of 150 patients with COVID-19, 7% of the first 68 reported deaths were attributed to myocarditis with hemodynamic instability, 5 cases of fulminating myocarditis were recorded among 27 myocarditis in 150 SARS-CoV-2 patients, 68 deaths of which 33% were mortality (37).

Infectious etiologies, especially viral ones, are not common in the case of acute myocarditis. (8). The latter is known for a long time as a secondary to heart, toxic, and allergic infections

or associated to a system disease (8 ,4). No data of the myocarditis prevalence in COVID-19 subjects are yet available, as well as the involvement of the virus in the myocarditis occurrence has not been confirmed (3).

Acute coronary syndromes

Patients with chronic coronary syndrome (CCS) who have COVID19 often have a poor prognosis. In these patients, cardiac functional reserve may be reduced due to myocardial ischemia or necrosis. When the patient is infected, heart failure is, therefore, more likely to occur, resulting in a sudden deterioration of the clinical condition. Some of the Chinese patients with COVID-19 in Wuhan had previously had coronary syndrome, which was associated with a more severe form of infection and high mortality (3). To date, no cases of SCA in a patient with COVID 19 have been published. However, a ruptured atheroma plaque can be used in patients in a severe stage of infection requiring special care compared to hospital care (38).

Cardiac arrhythmia

In a cohort of 137 patients at COVID-19, 7.3% had an acceleration of heart palpitations regardless of body temperature. Cardiac arrhythmia was also observed in more than 16% of hospitalized patients in a Chinese cohort (39). Unfortunately, no data on the type of cardiac arrhythmia likely to occur in covid19 subjects have yet been published. The high prevalence of cardiac arrhythmias could be attributed to metabolic disorder, hormonal stress, or hypoxia (2,40)

Heart failure

Heart failure and myocardial lesions were observed in 23% of patients with COVID-19 (21). It is currently difficult to determine whether this phenomenon is associated with a previous left ventricular dysfunction or the development of new cardiomyopathy (21,). It is imperative to think of myocarditis during malignant arrhythmia associated with an acute myocardial lesion (41).

Venous thromboembolic complications

Venous thromboembolic disease (VTD) is a nosological entity comprising two clinical presentations: deep vein thrombosis of the lower limbs (DVT) and pulmonary embolism (PE). It is more rarely manifested by cerebral venous thrombosis, upper limb, or mesenteric thrombosis (42).

Apart from the various factors predisposing to venous thromboembolic disease, COVID-19 infection is likely to cause intense activation of blood clotting, its mechanism is still unknown (43). It can be explained by the direct action of the virus on endothelial cells, hypoxia, SDR and the increased flow of pro-inflammatory cytokines (42,43). In addition, SARS-VOC-2 coagulopathy appears to be associated with an intense rise in D-dimers resulting from fibrin degradation. They are activation markers of blood clotting, and their high rate is usually linked to a poor prognosis. In an analysis published by Thrombosis Research and carried out in a cohort of 388 Italian patients. The presence of thrombus was detected in one-third of them (44).

The risk of VTC, in the case of COVID-19, remains poorly understood even though its prevalence is very high in critically ill patients (45). PE is the most common complication (n=25, 81%) (46). In a Chinese retrospective cohort of 81 intensive care patients, 20 patients or 25% had an ultrasound-confirmed PST (46.) Also, in another cohort of 184 Dutch patients followed at 2 weeks of their hospitalization in the intensive care, (IC 95%: 17-37) the cumulative probability of VTD is 27%, without routine screening but with thromboprophylaxis. In France, a prospective cohort of SDRA reports a proportion of 17% of VTD despite systematic thromboprophylaxis. It should be noted that the proposed treatments for COVID-19 can interact with anti-thrombotic drugs (1,47).

COVID 19 Treatment and CVD Interaction:

In the absence of a drug for SRAScov2, preventive measures such as social distancing, respect for hygiene conditions, healthy eating, sports, remain still the only solution to fight the disease while waiting for an effective therapy. However, in SARS-CoV-2 infection, hospitalized patients are subjected to a therapy protocol that may interact with cardiovascular drugs or cause cardiac toxicity (4,48).

- ***chloroquine/hydroxychloroquine***

Hydroxychloroquine is a molecule derived from chloroquine, used in the treatment of rheumatoid arthritis and lupus erythematosus thanks to its immunomodulatory and anti-inflammatory effects for decades (19). Recently, some studies show the antiviral role of chloroquine and hydroxychloroquine which consists in reducing the SARS-CoV-2 viral load and shortening its viremia duration (2,49).

The experimental tests of the French team of Dr. DIDIER RAOULT who demonstrated the promising therapeutic power of hydroxychloroquine against COVID19, by preventing the SARS-CoV-2 entry and exit in cells grown in vitro, thus effectively curbing its replication and spread (50). The hydroxychloroquine action is achieved through the reduction of the proinflammatory cytokine production and the activation of CD8 cells involved in immunity against SRAS- CoV-2 (2.50). Since then, this famous molecule has been widely controversial because of its health risks especially on the cardiovascular system compared to its beneficial effects in the treatment of COVID-19 (32).

Side effects of hydroxychloroquine range from mild's intestinal manifestations to serious cardiac complications (cardiomyopathy, conduction, and heart rhythm disorders such as auriculoventricular block, lengthening of the QTc interval, advanced twists, ventricular tachycardia, and ventricular fibrillation (51).

The different countries' views on the use of this substance in the COVID 19 treatment were not similar. In France, This protocol was widely criticized considering the limited number of patients in the study (26 patients at the beginning and 80 patients of which 3/4 recovered after 6 days after administration of hydroxychloroquine associated with azythromycin) and also that the study was not randomized (1.51),while in Morocco this protocol was adopted in all hospitals of the kingdom after an authorization by the Health Ministry from March 23th 2020 (1). In Belgium, the University Hospital of Liège also uses hydroxychloroquine (400 mg x 2) in case of COVID-19 (2).

Prolonged administration of hydroxychloroquine is likely to result (1.3,52):

- A risk of cardiac toxicity (toxic dose in adults is 2mg and lethal dose 2.5mg)
- Flattening the T-wave (at therapeutic doses)
- An elongation of the QT interval especially during an association with azythromycin
- Dilated restrictive cardiomyopathy.

Therefore, hydroxychloroquine therapy combined with azythromycin involves monitoring the Qtc by measuring ECG before starting treatment and then 3 to 4 hours

later, then twice a week (52). In the event of a reported cardiac complication, the reduction or even the cessation of treatment should be undertaken with the implementation of monitoring for the ECG stabilization. (2.53).

- ***Antiviral treatment***

Antivirals against COVID-19 are still being studied in relation to their effectiveness. Their principle is their ability to block the replication of the virus (54). This is ribavirin used in the treatment of hepatitis C and the remdesivir prescribed against Ebola and the couple lopinavir/ritonavir (7). The latter has long been used for the HIV treatment and acts directly by inhibiting viral replication. While Ribavirin and Remdesivir are competitive inhibitors of RNA polymerase virus (7.55). Ribavirin has varying effects on the warfarin plasma concentration, but so far it does not show any cardiovascular toxicity (55.56). On the other hand, lopinavir/ritonavir is responsible for extending the QT interval especially in patients with congenital QT syndrome or on treatment with drugs that lengthen QT, which can cause fatal arrhythmias (57). A QT interval is said to be long if it exceeds 440 ms in men and 460 ms in women (1). These antiviral drugs can alter the plasma concentrations of some drugs such as P2Y12 inhibitors and oral anticoagulants because of their interactions with CYP3A4. Lopinavir/Ritonavir increases plasma concentrations of ticagrelor, rivaroxaban and apixaban while decreasing plasma concentration of active metabolites of clopidogrel and prasugrel (1,57).

Conclusion

SARS-CoV-2 is generally known to be the cause of COVID-19 infection. However, it could be both a trigger for heart disease or worsening of a pre-existing cardiac condition. Since the beginning of the pandemic, research has multiplied to design an efficient and effective therapy that, based on available data, must take into account the magnitude of cardiac risk by adopting a preventive approach to reduce or even limit complications in COVID 19 patients with or without cardiovascular comorbidity.

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