Prevalence and impact of cardiovascular disease on COVID-19: A review

Prevalence et impact des maladies cardiovasculaires dans la COVID-19: Mise au point.

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Résumé

Introduction: La pandémie COVID-19 a provoqué des milliers de décès à travers le monde. Les patients souffrant d'une atteinte cardiovasculaire (CV) préalable représentent une population fragile .Pour les cardiologues, une compréhension adéquate de l'interaction entre COVID-19 et les maladies CV est nécessaire pour une prise en charge optimale de ces patients.

Objectif et méthodes : Cette mise au point évalue la prévalence des comorbidités cardiovasculaires chez les patients COVID-19 ainsi que leur impact sur le pronostic de cette maladie. Une recherche documentaire a été effectuée à l'aide des moteurs de recherche PubMed et Google pour préparer une revue narrative sur ce sujet.

Résultats : Les différentes études ont suggéré que les patients ayant un antécédent cardiovasculaire étaient plus à risque de développer des formes sévères d'infection par le SARS-CoV-2. En effet, 35 % des patients atteints de COVID- 19 avaient des antécédents d'hypertension artérielle et 17 % avaient des antécédents de maladies coronaires. Cette proportion est plus élevée dans les formes les plus sévères, avec une prévalence d'environ 50% pour l'hypertension artérielle, 22 % pour le diabète et 25 % pour la coronaropathie et l'insuffisance cardiaque. Plusieurs mécanismes sont évoqués bien que les mécanismes spécifiques soient encore incertains.

Conclusion : Cette contribution des maladies chroniques au fardeau imposé par la COVID-19 impose une attention particulière qui doit être accordée notamment à la prévention. Plusieurs études sont toujours nécessaires pour meilleure compréhension des mécanismes physiopathologiques.

Mots-clés
COVID 19, maladies cardiovasculaires, prévalence, morbi-mortalité

Summary

Background: The current COVID-19 pandemic was responsible for over one million infection worldwide and thousands of deaths. Adequate understanding of the interplay between COVID-19 and cardiovascular diseases (CV) is required for optimum management of these patients.

Aim and Methods: This brief review evaluates the prevalence of cardiovascular comorbidities among patients with COVID-19 and their impact on the prognosis of this illness. A literature search was done using PubMed and Google search engines to prepare a narrative review on this topic.

Results: The information about prevalence of CV comorbidities in COVID-19 is widely various across different geographic locations; Nonetheless, it has been consistently shown that CV disease was a common comorbidity; About 35% of COVID-19 patients had a history of hypertension and 17% had a history of coronary heart disease. This proportion is higher in the most severe forms of COVID-19, with a prevalence of about 50% for hypertension, 22% for diabetes and 25% for heart disease. The presence of pre-existing CV disease is then associated with significantly worse outcomes in these patients; several mechanisms have been mentioned.

Conclusions: This contribution of chronic CVDs to the burden imposed by COVID-19 requires particular attention mainly regarding prevention. Several studies are still needed to better understand the pathophysiological aspects.

Keywords
COVID 19-cardiovascular diseases, prevalence, morbidity

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INTRODUCTION

The coronavirus disease-2019 (COVID-19), is a newly recognized contagious infection that has spread rapidly throughout Wuhan, China in early December 2019.This highly contagious disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) that was responsible for a big challenge all over the world. In fact, COVID-19 has been declared as a pandemic by Word Health Organization (WHO)on March 11, 2020 [1].
As it spreads across the world, it has overwhelmed healthcare systems, strangled the global economy and led to a devastating loss of life.
Moreover, the number of cases fatalities owing to COVID-19 is escalating; SARS-CoV2 caused large numbers of deaths. There were about 2.661.506 confirmed cases of COVID-19 and about 185.504 deaths worldwide according to the situation report of WHO on April 24, 2020[1].
Common symptoms include fever, dry cough, fatigue and are dominated by respiratory symptoms, Nevertheless, some patients had severe cardiovascular damage [2]. In addition, emerging data suggests that patients with chronic cardiovascular diseases (CVDs) might have an increased risk of death. Thus, it is important for cardiologists and emergency physicians to be aware of the impact on the cardiovascular system as well as the clinical consequences of this drama and should react accordingly [2].
We here provide a review on two aspects related to COVID-19 as a disease: the prevalence of CV comorbidities among infected patients and the impact of these underlying CVDs on the prognosis and management of COVID-19 .

Search methods

A literature search was done using PubMed and Google search engines for original and review articles published since the onset of the current COVID-19 pandemic. Search terms: “coronavirus”, “COVID-19”, “SARS-CoV2 “and were used in combination with “cardiac”, “cardiovascular”, hypertension, diabetes, obesity, smoking, myocardial infarction”, “heart failure”,” coronary disease”, “drugs”, “therapeutics”.

RESULTS

*Cardiovascular system may get involved in several different ways: Here we focus on the impact of preexisting cardiovascular comorbidities on the incidence, the severity and the management of COVID19.Information may change and mature over time with increasing knowledge, changes in the pandemic and evidence from prospective studies.

SARS-CoV-2 pathogenesis:

**The cytokin storm :*

The pathogenic mechanism that produces COVID-19 damage is complex [3, 4] and not yet completely elucidated. There are several thoughts on the way of injury.
The data available seem to indicate that the viral infection produces an excessive immune reaction in the host. In some cases, this reaction described as “cytokine storm’ can result in injury to multiple organs leading to multi organ failure. In fact, studies have shown high circulatory levels of proinflammatory cytokines mainly TNF alpha, IL1 and IL6 in patients with critical COVID-19.
The virus would attack the targeting organs that express angiotensin converting enzyme 2 (ACE2), such as the lungs, heart, renal system and gastrointestinal tract [5, 6]; Spike protein (SARS-2-S) on the virus is activated by cellular serine protease TMPRSS2 highly expressed in lung, renal, and gastrointestinal cells and interacts with ACE2 that is highly expressed on respiratory epithelial cells which facilitates the entry of the virus into the host cell. (Figure1)[7]

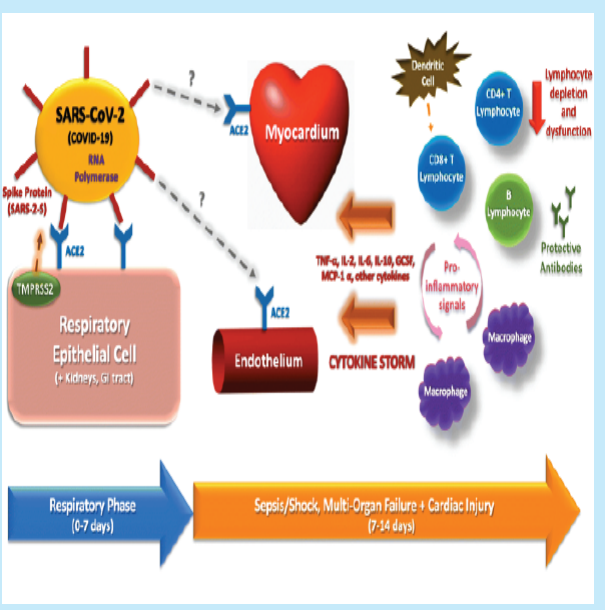

Figure 1 : Hypothesis of SARS-CoV-2 pathogenesis [7]

**The cardiovascular system injury:*

Cardiovascular complications associated with COVID-19 infection are a significant contributor to the mortality associated with this disease. These complications include myocarditis, heart failure, acute myocardial infarction, dysrhythmias, and venous thromboembolic events [8] .The patients admitted to intensive care unit (ICU) or having severe/fatal disease have higher likelihood to develop significant elevation of troponin. Acute cardiac injury has been shown to be a strong negative prognostic marker in patients with COVID-19 [9, 10]. For instance, Heart failure had occurred in 52% of deaths and in 12% of coronavirus cases who were discharged from the hospital.

Accumulated evidence suggests that cardiac involvement is common, and many mechanisms have been suggested: direct myocardial cells injury by the virus, atherosclerotic plaque disruption because of systemic inflammation and catecholamine surge inherent in this disease leading to acute coronary syndrome [11], myocardial oxygen supply/demand mismatch: hypoxia caused by acute respiratory illness can impair myocardial oxygen demand-supply relationship and lead to myocardial injury. Moreover, many therapies aiming at treating COVID-19 patients have harmful effects on the cardiovascular system (Figure2) [12].

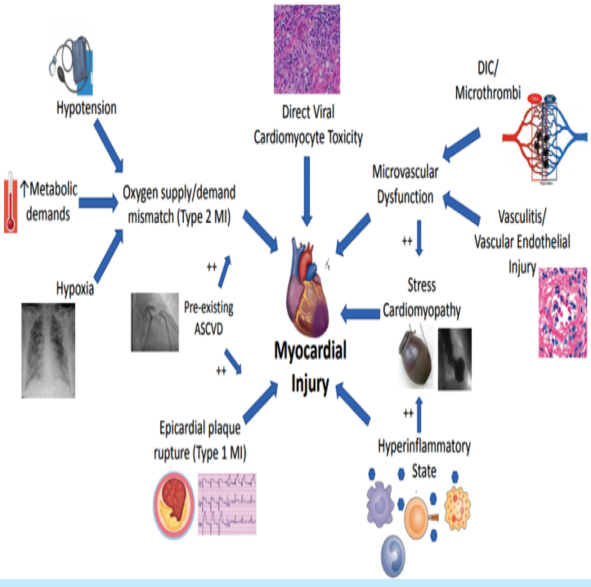

Figure 2: Potential Mechanisms of Myocardial Injury in COVID-19 [12]

ASCVD: atherosclerotic cardiovascular disease, DIC: disseminated intravascular coagulation, MI: myocardial infarction.

Endothelial cell infection and endotheliitis in COVID-19: A new challenging mechanism?

ZsuzsannaVarga et al [13] in their recent publication based on the analysis of 2 case reports found evidence of direct viral infection of the endothelial cell and presence of diffuse endothelial inflammation.The ACE2 receptor is in fact widely expressed on endothelial cells.

This suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement and this is responsible for the majority of damage. (Thromboembolism, respiratory distress, myocarditis, dermatological lesions, Acute coronary syndrome,). COVID-19 is far from simple viral pneumonia. The vascular system is then at the heart of the physiopathology of this disease.

**Pathogenesis in patients with preexisting cardiovascular disease:*

The theory of endothelial cell infection and endotheliitis in COVID-19 could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction; this is the case of smokers, male patients, obese patients, hypertensive patients and those with diabetes [13]. All of these situations are associated with adverse outcomes in COVID-19.

Role of underlying CV comorbidities: Greater risk of getting the infection? More severe illness?

Most of the patients with COVID-19 (80%) get a mild form of the disease. About 15% develop a severe form and require hospitalization. Critical form occurs in about 5% of patients needing intensive care. The mortality rate is between 2% to 5% of all cases [14].The most common causes of death are acute respiratory distress syndrome (ARDS), acute kidney injury and myocardial injury.

CVD was a common comorbidity in patients with COVID-19 predecessors

SARS and MERS [15].The increased presence of CV comorbidities holds true for COVID-19 as well, most notably among those with more severe disease. Studies did not find that people with hypertension, diabetes or coronary disease were more susceptible to COVID-19 infection. The prevalence of diabetes and hypertension in people infected with the virus is about the same as in the general population, even slightly lower [16].Nevertheless, patients with previous cardiovascular disease can greatly develop pneumonia with ARDS. The overall proportion of hypertension, cardio-cerebrovascular diseases and diabetes were about two fold, three folds and two folds, respectively, higher in severe cases than in their non-severe counterparts [16].

A report on 72.314 Chinese cases showed a mortality rate of 2.3% in all patients COVID-19 but this rate increases to 5% in patients with cardiovascular disease and to 7.3% in those with diabetes [17]. Prognostic significance of CVD was amply illustrated in the summary of Weiyi Tan et al about the cardiovascular burden of coronavirus disease 2019 (Figure3) [18] ; patients with hypertension accounted for 13% of the COVID-19 patients but they comprised 32% of the COVID-19 deaths. Patients with cardiovascular disease made up 4.2% of the COVID-19 cases, but were associated with 18.3% of the COVID-19 deaths. The meta-analysis of Wang et al [19] identified hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease as significant risk factors for COVID-19 patients. However the specific comorbidity by which can lead to disease progression remains unknown.

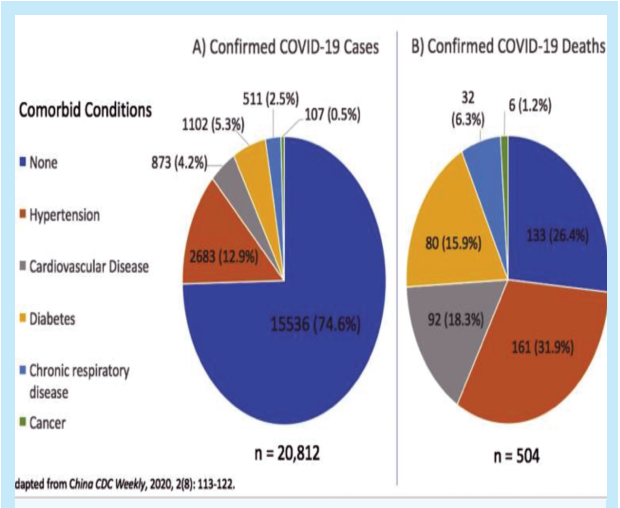

Figure 3: Proportion of patients COVID 19 and their comorbid conditions

Coronary artery disease was associated with increased odds (OR 21.4 [95% CI 4.64-98.7, p < .0001]) of death [20]This may be due to the fact that those with history of coronary artery disease may have impaired cardiovascular functional reserve and infection precipitates a myocardial infarction and worsen ischemia leading to heart failure and death.

Analysis of fatal SARS-CoV-2 cases in Italy revealed a prevalence of diabetes of 35% [21]. In a meta-analysis of 30 studies [22], diabetes mellitus was associated with poor outcome (mortality, ARDS, severe COVID-19and disease progression) and it was influenced by age and hypertension. The association was stronger in younger patients. Multiple potential mechanism may explain this frailty of diabetic COVID-19 patients, such as the proinflammatory state, and the attenuation of the innate immune response. There is also a metabolic concern; In fact, metabolic disorders may lead to low immune function by impairing macrophage and lymphocyte function [22].

Many reports have linked obesity to more severe COVID-19 disease and death. In a French study, the risk for invasive mechanical ventilation was more than seven-fold higher for those with Body Mass Index (BMI) >35 compared with BMI <25kg/m^2 [23].

What about smoking?

It was found a low incidence of daily active smokers in patients with symptomatic COVID-19.Thus, smoking status appears to be a protective factor against the infection by SARS-CoV-2 [24], Researchers hypothesize that the nicotinic acetylcholine receptor plays a key role in the pathophysiology and can represent a target for the prevention and control of COVID-19 infection [25].

Specific therapeutic strategies?

Once a patient with chronic cardiovascular morbidity is diagnosed with COVID-19, the management of the infection is similar to the general population. However, many of the therapies used to treat COVID-19 infection including antiviral (remdesivir, lopinavir/ritonavir), chloroquine, hydroxychloroquine and anti-inflammatory drugs (tocilizumab, steroids) have cardiovascular side effects. Thus, caution must be taken when applying them to patients with previous CV diseases.

This issue concerns the potential risk of cardiac arrhythmias with chloroquine or hydroxychloroquine mainly when combined with azithromycin particularly in critically ill patients and electrocardiographic QT interval monitoring with correction of hypokalemia and hypomagnesemia is highly recommended [26].

In patients with reduced ejection fraction a careful review of medical treatments should be considered; some molecules should be discontinued, other may be continued. Antiviral therapies can increase levels of beta-blockers warranting ECG monitoring and may modestly affect ACE inhibitors, while sacubitril/valsartan levels can increase, needing close monitoring of blood pressure .Spironolactone can be safely used with lopinavir/ritonavir whereas eplerenone, which is mainly metabolized by CYP3A4, should not be co-administered[27].

Association of ivabradine and lopinavir/ritonavir should be avoided. Digoxin levels should be followed closely in patients on antiviral drugs, hydroxychloroquine or

chloroquine. In addition, chloroquine may reduce levels of beta-blocker and require a dose up-titration. [28] There is no reported harm associated with statin use in these patients, which supports their continued use. The effect of ACE-inhibitors in patients with COVID-19 is not yet known and remains unproven. More studies are required to decide starting or withdrawing these drugs [29].

The most interesting Drug-Drug interactions with CV medications include:

*Hydroxychloroquine, Chloroquine: Beta-blockers, QTc prolonging agents

*Ritonavir/Lopinavir: Warfarin, direct oral anticoagulants (DOACs), Statins, P2Y12 inhibitors.

*Tocilizumab (IL-6 inhibitor):P2Y12 inhibitors, statins, DOACs, warfarin [30].

CONCLUSION

Patients with previous CV diseases appear to develop more severe COVID-19 infection with worse clinical outcomes and may greatly affect the prognosis of the illness. Although data is rapidly changing, rates of diabetes mellitus, hypertension and coronary artery disease appear to be higher among those with worse outcomes. But whether this is causal or simply an association remains one from areas of uncertainty of this challenging infection.

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