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Review

2019 novel-coronavirus: Cardiovascular insights about risk factors, myocardial injury, therapy and clinical implications

Luigi Cappannoli [1], Roberto Scacciavillani [1], Giulia Iannaccone, Gianluca Anastasia, Federico Di Giusto, Valentina Loria, Nadia Aspromonte*

Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy

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Abstract

From December 31st, 2019, a novel highly pathogenic coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide, reaching at present the dimension of a pandemic. In addition to damaging the lungs, SARS-CoV-2 may also damage the heart and this is corroborated by the evidence that cardiovascular comorbidities are associated with a higher mortality and poor clinical outcomes in patient infected by the virus. During the infection myocardial injury, myocarditis and arrhythmias have also been reported, but the pathophysiological mechanisms of these complications are yet to be understood. Great attention is also being posed on the potential beneficial/harmful role of angiotensin converting enzyme (ACE) inhibitors, as far as the virus binds to ACE2 to infect cells, but evidences lack. Furthermore, SARS-CoV-2 can also affect the aspect of acute coronary syndromes, not only because these two distinct pathological entities share pathogenic aspects (such as the systemic inflammatory state and cytokine release), but also and above all for the consequences that the need to contain the infection has on the management of cardiological urgencies. The aim of this review was therefore to summarize the relationship between the virus and the cardiovascular system.

Keywords: COVID-19; Cardiovascular; Angiotensin converting enzyme 2; Angiotensin converting enzyme inhibitors; Angiotensin-II receptor blockers

Introduction

From December 31st, 2019, several cases of severe pneumonia caused by a novel highly pathogenic coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been reported and from that day on the infection has spread worldwide, reaching the dimension of a pandemic.

In addition to damaging the lungs, SARS-CoV-2 also damages the cardiovascular system as suggested by the evidence that elderly patients with comorbidities

* Corresponding author. Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A, Gemelli IRCCS, Catholic University of Sacred Heart, Largo Agostino Gemelli 8, 00168 Rome, Italy.

E-mail address: nadia.aspromonte@policlinicogemelli.it (N. Aspromonte).

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[1] These authors contributed equally.

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are more likely to be infected by the virus and tend to have a more severe course if previously affected by hypertension, coronary heart disease, and diabetes. It is therefore important to analyze the relationship between the virus and the cardiovascular system.

Cardiovascular diseases and risk factors

The worldwide exact cardiovascular disease (CVD) prevalence in patients with the disease caused by the SARS-CoV-2, which was also called coronavirus disease 2019 (COVID-19), remains unknown both for the lack of widespread testing and for the absence of national and international data available. However, patients with cardiovascular comorbidities are more likely to present with severe manifestations of infection, especially those suffering from arterial systemic hypertension, diabetes and chronic coronary syndrome (CCS).[1,2] A recently published meta-analysis of six studies highlighted that hypertension, diabetes and cardio-cerebrovascular diseases are present in 17.1%, 9.7% and 16.4%, respectively in COVID-19 patients[3] and these comorbidities are also associated with a significantly higher overall case fatality rate compared to otherwise healthy patients.[4] Other studies confirmed this trend, showing indeed increased risk of poor clinical outcomes and higher death rates in patients with CV comorbidities.[5–7]

Myocardial injury, arrhythmias and myocarditis

Even if coronaviridae more often cause respiratory and gastrointestinal syndromes, their possible etiopathogenetic role in myocardial injury and myocarditis has previously been recognized for both SARS-CoV and MERS-CoV.[8,9] For SARS-CoV-2 this remains unproven, even if elevated levels of NT-proBNP and cardiac Troponin I (cTnI) are common findings in these patients.[10]

Myocardial injury is defined as an elevation of high sensitivity cTnI above 99th percentile upper reference limit and its possible pathophysiological mechanisms are different:

1. Direct myocardial injury. SARS-CoV-2 enters human cells by binding to angiotensin converting enzyme 2 (ACE2), leading to acute injury in tissues where it is expressed.[11] Even if the virus has still not been isolated in the cardiac tissue, it is believed to be associated with cardiomyocytes degeneration, inflammatory infiltrates in myocardial interstitium, vasculitis and microthrombi formation.[10]
2. Systemic inflammation. Cytokine storm observed in COVID-19 patients can result in injury to multiple organs leading to multiorgan failure.[12,13] Systemic inflammation is a well-known factor of plaque instability, being able to result in acute myocardial infarction. Corroborating the inflammatory hypothesis, the plasma interleukin 6 (IL-6) seems to be consistently increased in patient with COVID-19 and cardiac injury, often evolving in life-threatening arrhythmias and/or fulminant myocarditis.[14]
3. Hypoxia. Increased metabolic demand due the systemic infection and hypoxia caused by respiratory distress can impair myocardial oxygen demand-supply.

The incidence of acute myocardial cardiac injury in COVID-19 patients, previously reported to be 7.2%,[7] has recently been found to be much higher in two different studies,[15,16] with an incidence of 19.7% and 27.8% respectively. These studies also demonstrated that cardiac injury was independently associated with an increased risk of mortality and that COVID-19 patients with cardiac injury presented with more severe acute illness, worse radiographic findings and a higher risk for invasive ventilation. A recent metanalysis also suggested that there may be a correlation between the values of cTnI and the severity of clinical presentation: cTnI values were found to be significantly increased in COVID-19 patients with severe disease compared to mild-moderate cases.[17] These findings are compatible with acute myocardial injury being predictive of negative outcomes in COVID-19 patients.

In a case series, arrhythmias occurred in 16.7% of hospitalized COVID-19 patients. Both tachy- and brady-arrhythmias are possible and their incidence is higher (44.4%) in those patients requiring intensive cares.[7] Guo et al also reported that patients with elevated cardiac troponin levels developed more frequent malignant arrhythmias (11.5% *vs.* 5.2%), including ventricular tachycardia and ventricular fibrillation, compared to those with normal troponin levels.[16]

Coherently with the possibility that the virus is able to cause direct myocardial injury, several cases of myocarditis during COVID-19 have been reported; adding methylprednisolone to standard treatments was beneficial for these patients.[18,19] The autoptic presence of the virus in the myocardium of infected patients had already been proved for SARS-CoV,[20] and this is possible for SARS-CoV-2 too, although yet to be demonstrated. The most dangerous cardiac complication of COVID-19 is fulminant myocarditis, a rare clinical

entity with mortality rates of 40%–70%: in these cases, early diagnosis is crucial in order to provide patients with appropriate lifesaving therapies, including circulatory support systems to unload the myocardium.

Coronavirus disease, angiotensin converting enzyme 2 and ACE-inhibitors

The potential beneficial/harmful role of angiotensin converting enzyme inhibitors (ACE-i) or Angiotensin-II Receptor Blockers (AIIRBs) during SARS-CoV-2 infection is yet to be clarified. The enzyme ACE2, which is a homolog of ACE with different functions, is widely distributed in the lung, heart, kidney, and testis.[21] In SARS-CoV and SARS-CoV-2, the Spike protein (S) on the virus surface mediates receptor recognition and membrane fusion: the receptor binding domain (RBD) of S1 subunit directly binds to the peptidase domain (PD) of ACE2, while S2 subunit is responsible for membrane fusion.[22]

ACE-i and AIIRBs increase ACE2 expression and activity and, even if evidences lack, it has been hypothesized that this could increase viral load and worsen outcomes.[23] On the other hand, ACE2 degrades Angiotensin II (Ang II) to Ang 1-7, hence diminishing Ang II receptor 1-mediated deleterious effects of systemic inflammation and that could diminish COVID-19 associated lung injury.[24]

A trial on the delivery of excessive soluble forms of recombinant human ACE2 (rhACE2) in SARS-CoV-2 infected patients (NCT04287686) has recently been proposed; it is reasonable to think that this approach wouldn't have a great impact in preventing the respiratory infection but rather it may be protective against viral systemic dissemination and severe inflammatory complications, as previously suggested by a pilot study of rhACE2 in ARDS patients.[25] Furthermore, a retrospective analysis performed on 112 COVID-19 patients did not reveal a significant difference in the proportion of ACE-i/AIIRBs medication between the critical group and the general group or between non-survivors and survivors.[26]

Therefore, the role of ACE-I and AIIRBs remains controversial, but due to lack of evidences discontinuation of renin-angiotensin system inhibitors because of COVID-19 infection is discouraged, as stated by the European Society of Cardiology[27] and by the American College of Cardiology, American Heart Association and Heart Failure Society of America.[28] This is particularly true for diabetic patients, who are at the same time considered at risk for COVID-19[29] and also often treated with an ACE-i or an AIIRB (due to hypertension, cardiovascular or renal damage): it would be incautious to stop these helpful drugs for this kind of patients almost until we can dispose of further evidences on this controversial aspect.

COVID-19 and acute coronary syndrome

Acute coronary syndromes (ACS) associated to SARS were reported during the 2002–2004 epidemic of SARS-CoV-1.[30] To our knowledge there have not yet been any reports of myocardial infarction directly caused by COVID-19, but even if these two pathological entities have different etiologies, they share common pathogenetic features and the systemic involvement of SARS has direct and indirect effects on the coronaries and on the phenotype of acute coronary syndrome and myocardial infarction that may occur.

Host inflammatory response can lead to acute systemic inflammatory state and massive cytokine release, largely mediated by proinflammatory granulocytes and macrophages,[31] and this is a well-known strong independent predictor of poor outcome in patients with severe COVID-19, resulting in multiple organs injury.[12,13] Moreover, increased blood flow through the coronary system associated with systemic inflammation may result in increased shear stress, triggering plaque rupture in a process where dysregulation of the coagulation system and prothrombotic state further increase the risk.[32,33] Furthermore, hypoxia caused by acute respiratory distress and increased metabolic demand resulting from the inflammatory response may have major additive detrimental effects on the heart impairing the myocardial oxygen demand/supply relationship. All these factors may have different roles during different times in natural history of the disease, further destabilizing a coronary milieu where thrombotic and hemodynamic determinants are already unbalanced.

Clinical implications

At present, it has not been described the prevalence of cardiac complications in patients naïve for cardiovascular disease versus COVID-19 patients with cardiac comorbidities. As highlighted by the American College of Cardiology, it is mandatory to promptly individuate high risk patients and to monitor clinical signs and symptoms of cardiovascular disfunction and to pay attention to blood biomarkers of myocardial injury, heart failure and systemic inflammatory response.[34]

Moreover, symptoms like dyspnoea are common between heart and lung failure, thus leading to potential misdiagnosis and delayed infection identification.

In doubtful cases, epidemiological history and fever or respiratory symptoms can help, together with a careful chest computed tomography analysis.[35]

Therefore, it seems that during this pandemic cardiologists have to face multiple challenges: on one hand there is the necessity to contain the spread of the infection, on the other there is the increasing difficulty in identifying and treating patients with suspected or confirmed COVID-19 and contemporary cardiological urgencies; protocols are being constantly refined and updated but clinical judgement will be fundamental too. Patients with STEMI and suspected infection are for example suggested to be studied in cath-labs only if at high cardiological risk, while they should be treated with thrombolysis if at low risk.[36] Although this may be useful in the immediate to contain the pandemic, the consequences of these new approaches are uncertain, and we will have evidence of this in the next future.

Conclusions

COVID-19 patients share many characteristics with patients with cardiovascular diseases, and this can on the one hand pose problems of differential diagnosis and on the other explain why the infection is more serious precisely in patients with underlying cardiovascular comorbidities. Current COVID-19 pandemic infection then leads us, once again, to consider the close relationship between cardiovascular disease and inflammation. Cardiovascular patients have often a systemic inflammatory background which is already known to be a central trigger of plaque instability and a negative prognostic marker in patients with ACS. The severity of clinical manifestations of many pathologies, as well as for COVID-19, could therefore depend on the individual's inflammatory response rather than on the pathogen itself and this would explain the presence of elevated blood levels of inflammatory cytokines, including IL-6, in patients with more severe forms of COVID-19. These findings have not only important pathogenetic implications, but also therapeutic ones, as evidenced by the promising results obtained from the use of anti-rheumatoid drugs for the treatment of COVID-19.

Conflicts of interest

None.

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