EDITORIAL

COVID-19 AND CARDIOVASCULAR STORM

COVID-19 pandemic is one of the biggest challenges confronting communities and nations, having a tremendous impact on public health services all over the world. In the past years, people have faced several worldwide epidemic infections, such as Severe Acute Respiratory Syndrome (SARS), avian influenza, influenza, but SARS-Cov-2 is rapidly becoming the most threatening global enemy, endangering not only the health systems' stability, but transforming into a social and economic crisis.

SARS-CoV-2 is part of a group of viruses, including severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) (1), well known in the past two decades and infecting almost 9,000 people worldwide (2).

Coronaviruses are single stranded RNA, presenting (when symptomatic) with almost the same symptomatology, consisting of fatigue, fever, and dry cough at the beginning (3). The severity of symptoms, alone or in combination with modified blood biochemistry represent prognostic markers in COVID-19 patients (4) and they may vary from absence of symptomatology or mild pneumonia to severe respiratory impairment: dyspnea, tachypnoea, low blood oxygen saturation or lung infiltrates in 24-48 hours.

The severity of lung injury may lead rapidly to acute respiratory distress syndrome (ARDS), an entity that is usually associated with high mortality rates since the early reports from the American-European consensus conference in 1994 (5), despite new ventilation protocols with new generation of ventilators.

The ARDS evolution may be complicated by respiratory failure, septic shock, or multiple organ dysfunction with an increased risk of death. Moreover, studies suggested that in ARDS, cardiovascular complications such as fulminant myocarditis and vascular thrombotic events should be considered (6).

COVID-19 and cardiovascular complications

The thrombogenic status in COVID- 19 creates the premises of developing pulmonary thromboembolism, acute myocardial infarction, or strokes. Since February 2020, several studies reported a high incidence of myocardial involvement in critically ill patients with COVID-19 with or without previous cardiac impairments (7).

Previous conditions may represent risk factors for the infection with the new coronavirus (8), data confirmed also in a systematic review that included 41 studies and 27670 patients which demonstrated the higher risk of death in patients with preexisting cardiovascular diseases, immune and metabolic disorders, respiratory diseases, neoplasia, cerebrovascular, renal, and liver diseases (9).

The main target of SARS-CoV-2 is represented by ACE2 receptors, that are highly expressed in the lungs and heart, a mechanism that rapidly became controversial in terms of using or not Angiotensin Conversion Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) in COVID-19 hypertensive patients. This discussion was clarified by the most recent guidelines recommendations, which stated that the use of ACE inhibitors is safe and

should be continued as indicated (10).

In a systematic review and meta-analysis that analyzed 27 studies with 10197 patients taking renin-angiotensin drugs in COVID-19 there was nonsignificant associations between ACEIs/ARBs and death or ICU admission, risk or severity of SARS-CoV-2 infection and hospitalization, but a significant association between RAAS drugs usage and hospitalization was found, in the subgroup analyses of the United States of America included studies (11).

Furthermore, there are several studies that show higher rates and severity of the infection in men versus women due to a higher expression of proteins that bind the virus and genome disparities (12), meanwhile a study performed in the United States of America revealed racial and ethnic disparities, African American/Black and Hispanic populations having a higher rate of SARS-CoV-2 infection and mortality compared with non-Hispanic White population, but with similar rates of case fatality (13).

COVID-19 and
acute coronary syndromes

When acute coronary syndromes are taken into consideration, the endothelium plays a major role. It provides normal vascular homeostasis by regulating vascular tone, cells adhesion, thrombosis, and inflammation, meanwhile lymphocytes represent a major regulatory point in maintaining homeostasis and against exaggerated inflammation after infection (14).

Therefore, due to the intense activation of endothelium caused by a high number of cytokines associated with low levels of T-lymphocyte lines, the COVID-19 patients present an increased prothrombotic status associated with an intense inflammatory response (15).

The magnitude of the inflammation is well corelated with the cardiac involvement, which can be revealed by high levels of troponin and NT- pro BNP at admission. In consequence, these patients present a high risk of coagulopathy, heart failure or a mortality up to 50% (16).

Other biomarkers that can be used for therapy efficiency are endothelial extracellular vesicles (17) and endothelial progenitor cells, that can be also correlated with disease severity (18) and with vascular injury (19).

It is well known that atherosclerosis and inflammation represent important risk factors in developing acute coronary syndromes (20). But several studies also reported a relation between acute coronary syndromes and COVID-19 caused by coronary artery thrombosis, even without a pre-existing atherosclerotic lesion or with nonobstructive lesions (21), most likely due to microvascular involvement (22).

A study that included 305 patients with COVID-19 from 7 hospitals in New York City and Milan illustrates the significance of the cardiac involvement. Thereby, from the 305 patients included, 190 had evidence of myocardial injury and from them 26.3% had right ventricular dysfunction, followed by 23.7% with left ventricle wall abnormalities, 18.4% with left ventricle global dysfunction, 13.2% with diastolic dysfunction grade II or III and 7.2% pericardial effusions (23).

In terms of paraclinical methods, these patients require classical echocardiography, but cardiac MRI mapping techniques are particularly useful providing evidence of diffuse myocardial infiltration even in asymptomatic cases (24).

Regarding the acute coronary syndromes therapy strategies, the ESC Guidance for the Diagnosis and Management of Cardiovascular Disease during the COVID-19 pandemic stipulates that the invasive cardiac procedures in emergency situations, such as ST-

elevation acute myocardial infarction, non-ST elevation acute myocardial infarction in very high risk and high-risk patients and also in cardiogenic shock must not be postponed. The reperfusion therapy remains unchanged in terms of strategy in STEMI patients that must be managed as if they are COVID-19 positive in the absence of a previous RT- PCR test for SARS-Cov-2.

The reperfusion therapy remains the primary PCI, with a maximum delay from diagnosis to reperfusion of 2 hours, procedure that may be delayed no more than 60 minutes due to care and protective measures implementation. Fibrinolysis will be maintained as second option if the reperfusion target time cannot be achieved and if it is not contraindicated (25).

COVID-19 and arrhythmias

Several studies demonstrated the presence of cardiomegaly and right ventricle enlargement in COVID- 19 patients, with the presence of arrhythmias caused probably by myocardial infiltration and severe inflammation linked to ion channel dysfunction and both electrophysiological and anatomical remodeling (26).

Besides these, adding the pharmacological agents that COVID- 19 patients require, antiviral drugs such as Hydroxychloroquine and Azithromycin that are well known to prolong QT interval, requires a special attention. Repeated ECGs, electrolytes balance and kidney function are necessary and the combination with Amiodarone should be avoided. Moreover, all modifiable QTc prolonging factors must be corrected, including kalium and calcium levels, magnesium supplementation and bradycardia avoidance, with the necessity of ceasing concomitant QT- prolonging drugs if needed (23).

On the other side, elective procedures such as ablation or cardiac device implantation should be postponed, urgent procedures being performed only in exceptional cases.

COVID-19 and myocarditis

Myocarditis is well known to provide heart failure and sudden cardiac death (27), being also potentially caused by COVID-19.

There are four presumed mechanisms that may explain the cardiovascular involvement in COVID-19: a direct viral effect against cardiomyocytes, myocardial interstitial fibrosis, secondary hypoxia induced by pulmonary impairment and the inflammatory immune response that generates the cytokine storm (28).

Fulminant myocarditis represents a high mortality cardiac condition, in some registries with a short-term survival rate of only 58% (29), but with a higher long-term survival after discharge rate reported in some retrospective studies compared to non-fulminant myocarditis forms (30).

Chen *et al.* observed that in their center, which treats critically ill patients with SARS CoV-2 complicated by severe cardiac injury, the main cause of death was fulminant myocarditis. From the 120 patients included in the study, 27,5% had high levels of NT-pro BNP and 10% c Tn I (6).

In SARS-Cov-2 infection the virus binds on ACE2 receptors located in the myocardium and the endothelium, sometimes developing an overwhelming immune reaction that can lead to cytokine storm, with powerful damage of the endothelium that leads to multiorgan failure and death (31).

The risk factors and incidence of myocarditis in COVID-19 are still unclear, patients receiving in these cases anti-inflammatory therapy alongside with high dose parenteral glucocorticoid or even immunoglobulins, but standard care therapy may reach its limits, therefore mechanical circulatory support therapy may be neces-

sary for these patients. Adding venous-arterial ECMO (V-A ECMO) to standard therapy may cause a positive impact on patient's survival.

The first case of COVID-19 complicated by fulminant myocarditis reported in China was a male patient with high levels of troponin I, and NT pro BNP, with diffuse myocardial dyskinesia and a low left ventricular ejection fraction, successfully recovered after 3 days on ECMO (32).

Also, myocardial injury may be present even in convalescent patients with no previous cardiac symptoms or conditions (33).

In case of cardiogenic shock, if there is a suspected or positive COVID-19 patient, the European Society of Cardiology recommends prioritizing the health- care workers' protection, being also more restrictive with mechanical circulatory support; however, if needed, the use of ECMO should be considered. In case of negative COVID- 19 patients they will be treated as usual.

COVID-19 and pulmonary embolism

Even if pulmonary embolism is an uncharacteristic evolution of COVID-19, more patients present at the time of admission with both pathologies, coincidental or not (34).

The signs that must alert the medical team of an acute onset of a pulmonary embolism can be a sudden respiratory worsening, the occurrence of a new tachycardia , hypotension, hypovolemia or sepsis and ECG changes suggestive for pulmonary embolism or deep vein thrombosis signs revealed on clinical examination.

In a systematic review of 42 studies enrolling 8271 patients, deep vein thrombosis was found in 20% of the COVID-19 patients, meanwhile pulmonary embolism occurred in 13% of the cases. The study concluded with a pooled mortality rate of 23% in patients with thromboembolism versus 13% in patients without thromboembolism, showing an increased risk of death in COVID-19 associated with this complication (35).

The incidence of pulmonary embolism seems to be higher that it was thought and is revealed also in a study that analyzed 3011 patients, being the most common condition, with 198 cases (6.6%), followed by 55 patients with heart failure, 15 acute coronary syndromes, 14 ventricular arrhythmia, 4 endocarditis and 3 myocarditis. Even though the study showed a low incidence of cardiac complications during hospitalization (36), the high rates of pulmonary embolism must alert the medical team in a fast diagnosis and treatment in these patients. Another evidence showed the magnitude of venous thromboembolic embolism in COVID patients, translated in terms of survival, the incidence of severe condition being more likely to occur, especially in those with lower levels of lymphocytes (37).

But since other studies reported similar in- hospital mortality in critically ill COVID-19 patients with or without the presence of pulmonary embolism (38), further prospective randomized studies are needed.

The most common measures that must be taken in embolism prevention is to consider anticoagulation at standard prophylactic doses in all COVID- 19 patients. Also, due to several possible interactions between non-vitamin K antagonist oral anticoagulants (NOACs) and antiviral drugs such as Lopinavir or Ritonavir, the use of NOACs must be avoided, preferring the use of heparins instead. The risk stratification is accordingly to the current ESC guidelines.

Ongoing randomized clinical trials still represent the most powerful tool to provide high quality clinical care and offer best opportunities to manage the pandemic crisis and they started offering us the hope that we needed.

CONCLUSIONS

COVID-19 still represents a difficult enemy to deal with, but in the past weeks we started to see the light over horizon by developing vaccines and by continuously analyzing best specific and supportive treatments for the SARS-CoV-2 infection.

An important lesson learnt from the COVID-19 pandemic is that there must be a conjugated effort from the Heart Team, that now includes the infection disease doctor and the epidemiologist, in eradicating this virus and assuring the patient survival.

Only a persuasive collaboration between the entire medical team, patients, and health public policies alongside with every single social and economic aspect that is to be improved, may shape the victory against any health menace that may endanger humanity.

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