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How Stable Ischemic Heart Disease Leads to Acute Coronary Syndrome in COVID-19?

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Abstract. Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the increased mortality risk of patients with underlying cardiovascular diseases and COVID-19 was raised. Besides, coronavirus itself enhances the incidence of myocardial injury, which suggests a two-sided relation. We aimed to discuss the role of COVID-19 in the progression of stable coronary artery disease (CAD) to acute coronary syndrome (ACS), which might lead to a greater rate of out-of-hospital cardiac arrest and a higher fatality rate of ACS during the pandemic. We briefly reviewed several mechanisms in this regard: Systemic inflammation and cytokine release in critical patients; Plaque rupture and coronary thrombosis; Dysregulation of cytotoxic T-cell lymphocytes; Malignant ventricular arrhythmias. We reinforce applying more attention to COVID-19 patients with stable CAD during follow-up to prevent progression to ACS. These individuals should seriously observe World Health Organization protocols to avoid virus transmission by carriers. (www.actabiomedica.it)

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2, Coronavirus Disease 2019, COVID-19, Acute Coronary Syndrome, Coronary Artery Disease, Stable Ischemic Heart Disease, Stable Coronary Artery Disease, Out-of-Hospital Cardiac Arrest

Introduction

Coronavirus disease 2019 (COVID-19), which resulted from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a global pandemic in late 2019 (1). The worldwide progression of COVID-19 is changing day by day, while more than 60 million cases have been affected from almost all countries and territories in one year. Studies demonstrated that cardiovascular diseases and risk factors are associated with a greater risk of mortality and poorer outcomes in COVID-19. Investigators showed that a past medical history of coronary artery disease (CAD) increases in-hospital death in patients with COVID-19 by 2.25 (95% confidence interval: 1.60 to 3.17) (2).

Challenge

Studies showed that the incidence of out-of-hospital cardiac arrest (OHCA) increased during the COVID-19 pandemic. In the first two months of the COVID-19 outbreak in Northern Italy in 2020, the OHCA incidence rose by 52% in comparison to the same period in the previous year. OHCA victims with confirmed or clinically suspected COVID-19 accounted for 74% of the excess number of OHCA cases (3). Furthermore, an observational study revealed that the fatality rate of ST-elevation myocardial infarction increased from 4.1% in 2019 to 13.7% in the pandemic era in 2020 (4). These findings raised the dilemma that people who suffer from chest pain may not seek medical attention (5),

or COVID-19 possibly transforms stable CAD to acute coronary syndrome (ACS) (6). Some studies concluded that ACS admission was significantly decreasing during the pandemic, indicating fewer patients referred to the hospital (7); however, we cannot rule out the interaction between SARS-CoV-2 and CAD. In this communication, we aimed to discuss the role of COVID-19 in the progression of stable CAD to ACS, which might lead to the greater rate of OHCA and the higher fatality rate of ACS during the pandemic. Moreover, we briefly reviewed the possible mechanisms.

Mechanisms

Endothelial Dysfunction

In the physiologic conditions, the endothelial cells maintain tonic vasodilatation of vessels by producing nitric oxide via endothelial nitric oxide synthase and secretion of prostaglandin I2 (PGI2) (8). Some mechanisms can interfere with endothelial-dependent vasodilatation. For instance, the endothelial cell can produce one of the most potent vasoconstrictors known, endothelin-1, in response to angiotensin or thrombin. While key in maintaining normal vascular homeostasis, during disease, the salutary endothelium's functions can give way to inappropriate vasoconstriction contributing to tissue ischemia. Pro-inflammatory cytokines can induce endothelial cells to change from their homeostatic activity to the condition that can contribute to thrombosis and local tissue injury. Cytokines such as interleukin-1α (IL-1α), IL-1β, IL-6, and tumor necrosis factor α (TNFα) contribute critically to normal host defenses; nevertheless, their inappropriately excess production can disrupt all of the carefully orchestrated protective functions of the healthy endothelium and potentiate pathological processes. This untrammeled production of pro-inflammatory cytokines contributes to a condition termed cytokine storm (9). Besides, IL-1 produced by endothelial cells and invading leukocytes can elicit the production of chemoattractant molecules, including the chemokines that mediate the penetration of inflammatory cells into tissues. Hence, the pro-inflammatory state in COVID-19 and the consequent endothelial dysfunction (10) may play a role in the progression of the pre-existent CAD to ACS.

Plaque Rupture

Studies underscored the importance of macrophages in COVID-19. They secrete collagenase that destroys collagen, a major component of the fibrous cap on atherosclerotic plaques, which can lead to plaque rupture. Furthermore, they release tissue factor, a potent pro-coagulant that triggers thrombus formation when the plaque ruptures (11). Therefore, SARS-CoV-2 infection can transform stable CAD to ACS.

Cytotoxic T-Cells

Apart from the rupture of the fibrous cap of the plaque in the progression of stable CAD to ACS (RFC-ACS), which is the most well-known mechanism, ACS with intact fibrous cap (IFC-ACS) accounts for one-fourth of cases with ACS (12). Although the main pathophysiological mechanisms are still undefined; some novel hypothesis has been suggested.

In a recent study, investigators found that culprit lesions in IFC-ACS are more enriched in T-lymphocytes, especially cytotoxic CD8+ T-cells, compared to culprit lesions of RFC-ACS. Moreover, effector molecules of these cells, including granulysin, perforin, and granzyme A were more concentrated in IFC-ACS lesions rather than RFC-ACS lesions. Hence, these recent findings recommend a role for CD8+ T-cells in IFC-ACS (13); nonetheless, the role of macrophages in RFC-ACS has been established previously (14).

Since COVID-19 is a viral infection in which CD8+ T-cells are responsible for host defense, the possible role of CD8+ T-lymphocytes in converting stable plaque to IFC-ACS is raised.

Hypercoagulable State

The well-known mechanism that induces ACS in the context of stable CAD is the micro-thrombi resulted from the hypercoagulable state. In the context of COVID-19, hypercoagulability can arise from systemic inflammation or cytokine storm in critically ill patients, the direct endothelial or vascular injury by SARS-

CoV-2, increased pro-coagulant factors including fibrinogen, and factor VIII (11, 15). Another possible proof for the presence of the hypercoagulable state in COVID-19 may be the high prevalence of thromboembolic diseases in autopsies of patients with COVID-19, and the lower mortality rate and better outcomes of patients with COVID-19 who received either prophylactic or therapeutic doses of anticoagulants.

Myocarditis and Direct Myocardial Toxicity

Direct myocardial injury appears when coronavirus binds to its receptor angiotensin-converting enzyme 2 (ACE2) in cardiac cells and enters the myocytes (16). This process can lead to myocarditis that by increasing cardiac demand might enhance the possibility of converting stable CAD to ACS.{Lang, 2020 #210}*{Lang, 2020 #210}* The converted myocardial demand-supply ratio is a situation when an increase in cardiometabolic demand related to the systemic infection and hypoxia due to the acute respiratory illness can impair the myocardial oxygen demand-supply relationship and lead to myocardial injury. Furthermore, tachyarrhythmia, such as ventricular tachycardia, as a complication of myocarditis, might happen that increases the probability of OHCA occurrence (17).

Tachyarrhythmia

The SARS-CoV-2 infection results in the secretion of inflammatory cytokines including IL-1, IL-6, and TNFα, which leads to the blockage of cardiac potassium channels, QT prolongation, and in turn increases the risk of malignant ventricular arrhythmias and OHCA (18). Moreover, electrolyte imbalances that happen in any severe systemic illness can lead to arrhythmias, typically in patients with underlying cardiac disorders. There is a particular hypothesis about hypokalemia because of the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system (19).

Conclusion

In this study, we briefly reviewed several mechanisms that lead to convert the pre-existent CAD to ACS in COVID-19: Systemic inflammation and cytokine release in critical patients that leads to mul-

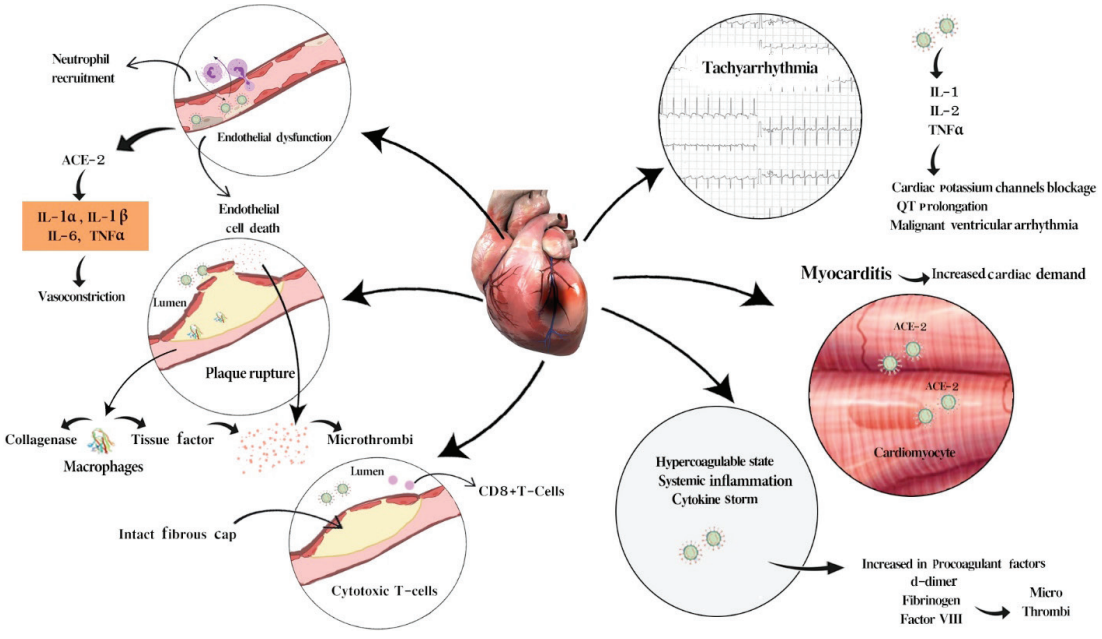

Figure 1. Mechanisms for progression of stable CAD to ACS in COVID-19. Six different mechanisms are shown including 1) Endothelial dysfunction; 2) Plaque rupture; 3) Activation of CD-8+ T cells in the intact fibrous cap; 4) Hypercoagulable state; 5) Myocarditis and direct myocardial toxicity; 6) Tachyarrhythmia.

ti-organ dysfunctions and endothelial dysfunction; Plaque rupture and coronary thrombosis in which inflammation create pro-coagulant factors (19); Dysregulation of cytotoxic T-cell lymphocytes converts stable plaque to IFC-ACS (13); Malignant ventricular arrhythmias, the SARS-CoV-2 infection results in the secretion of inflammatory cytokines such as IL-1, IL-6, and TNFα, which leads to the blockage of cardiac potassium channels and QT prolongation (figure 1).

Furthermore, we highlighted the higher mortality rate of COVID-19 in patients with cardiovascular disease. Therefore, we recommend clinicians to put a high focus on patients with CAD in the pandemic era. Recent studies showed that the restructuring of hospital services to cope with an influx of COVID-19 cases, combined with social distancing measures, has severely limited access to cardiovascular care, adversely impacting patient outcomes (20). Hence, we reinforce applying more attention to COVID-19 patients with stable angina during follow-up to prevent transformation to ACS. These individuals should seriously observe World Health Organization protocols to prevent virus transmission by carriers. Pharmacological thrombosis prophylaxis in hospitalized patients with COVID-19 might be beneficial (21).

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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