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A Review of Coronary Artery Thrombosis: A New Challenging Finding in COVID-19 Patients and ST-elevation Myocardial Infarction

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Abstract: As the COVID-19 pandemic continues, more information on the nonrespiratory effects of the coronavirus is obtained. Cardiovascular complications, especially acute coronary syndromes, are rare. However, they prove to be effective factors in the mortality rate of COVID-19 subjects. Acute ST-elevation myocardial infarction with a special angiographic pattern in the form of extensive and multivessel thrombosis, regardless of atherosclerotic plaques, has posed a new therapeutic challenge. This has been associated with an increase in the incidence of stent thrombosis. Hypercoagulation, due to severe inflammation, is the main pathology of this phenomenon. Technically, percutaneous coronary intervention with aspiration thrombectomy and injectable antiplatelet are the mainstay of treatment for these patients. In addition, it is vital that appropriate antiplatelet and ischemia treatment after the intervention be taken into account. (Curr Probl Cardiol 2021;46:100744.)
Introduction

People all over the world have been fighting the coronavirus pandemic called COVID-19 almost for a year now, and the second peak of this disease has already started in some countries. According to the latest statistics published by the World Health Organization (WHO) on August 16, 2020, 21,294,845 people have been infected, 761,779 of whom have died due to the COVID-19. The clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are fever, myalgia, anorexia, and respiratory symptoms such as shortness of breath and dry cough. However, recent reports indicate more severe manifestations and conflicts such as gastrointestinal and neurological disorders. It is worth mentioning that one of the vital and relatively rare nonrespiratory manifestations in these patients is cardiovascular disease. Cardiovascular damage in these patients includes myocarditis, acute coronary syndrome (ACS), arrhythmia, stroke and venous thromboembolic diseases. The ambiguous issue regarding cardiovascular disease in these patients is the occurrence of ACS, which either directly or indirectly plays a significant role in morbidity and mortality. In fact, the main challenges in the medical management of patients with COVID-19 and ACS are the choice of treatment method, capacity and facilities of medical centers such as the availability of catheterization laboratory and patients transfer conditions. ST-elevation myocardial infarction (STEMI) is the most important component of ACS during COVID-19 pandemic, and more recently, it has been reported in reports as the first manifestation of patients with COVID-19 or in the course of treatment of this viral infection. Apart from the challenge of choosing the right treatment strategy for these patients (primary percutaneous coronary intervention (PCI) vs fibrinolytic therapy), the angiographic pattern of these patients which is based on the presence of significant coronary artery thrombosis is a matter of contention for us as well as cardiologists.

Basic Concepts and Epidemiology

Analysis of studies related to influenza outbreak and viral pneumonias has illustrated that cardiovascular diseases, especially myocardial infarction (MI), have played a significant role in helping patients to survive. Previous studies have shown a 10% to 30% prevalence of cardiovascular events in patients with influenza and viral pneumonia. Nevertheless, these statistics vary slightly in different studies. Unfortunately, no precise and reliable information has been reported on the prevalence of cardiovascular events, especially ACS, in patients with COVID-19. Our basic
information is about the incidence of acute myocardial injury in patients in China. Having conducted a prospective study on 416 patients with COVID-19 in Wuhan, Shi et al reported 82 acute myocardial injury cases (19.7%). On the other hand, in the study of Zhou et al and Huang, these statistics were 17% and 12%, respectively. In a separate analysis, Wang et al reported a prevalence of 7% in all patients with COVID-19 and 22% in patients in need of intensive respiratory care. Acute myocardial injury does not necessarily coincide with the onset of myocardial ischemia and is diagnosed as a severe myocardial inflammatory injury with positive cardiac biomarkers such as troponin. As a matter of fact, elevated troponin levels are directly related to the severity of COVID-19 disease, making the prognosis of these patients even worse, especially when the symptoms and evidence of myocardial ischemia emerge.

Acute coronary syndromes are classified into 2 general categories called non-ST-elevation myocardial infarction (non-STEMI) and STEMI, with the most cases of acute myocardial injuries falling into the Non-STEMI category if there is evidence of ischemia. The vast majority of ACS patients are candidates for medical treatment based on clinical risk, and only very high-risk Non-STEMI cases and STEMI patients require taking an interventional approach. Our statistics related to incidence of STEMI are mostly in the form of case reports, and therefore, the epidemiology cannot be stated precisely. During a 40-day study in Lombardy, Italy, from February 20 to March 30, 28 cases of STEMI were reported, 24 of which (85.7%) reported STEMI as the first manifestation of COVID-19 before polymerase chain reaction (PCR) testing. In a retrospective multicenter study conducted in Italy, Lithuania, Spain and Iraq, 78 patients were diagnosed with STEMI and COVID-19 in 75 days. In this study, the final outcome of patients and their treatment methods were subjected to close scrutiny.

**Pathology**

Coronary artery angiography (CAG) in patients with COVID-19 and STEMI showed huge thrombosis with both obstructive and nonobstructive atherosclerotic plaque patterns. Accordingly, the detection of STEMI in patients with COVID-19 is either affected by atherosclerotic plaque rupture, spontaneous thrombosis formation or a combination of these 2 phenomena. With regard to the report published by Rey et al, thrombotic involvement of 2 RCA and LAD vessels was described simultaneously in a patient with COVID-19 and Inferior MI. Nonetheless, in another infero-lateral MI case, this finding was reported as a large
occlusive thrombosis in both LAD and RCA vessels by Kurdi et al. As a result, coronary arteries were evident in their patient without atherosclerotic plaque. Furthermore, extensive thrombotic involvement of several coronary arteries has also been reported by Dominguez-Erquicia and Setia. As a matter of fact, the SARS-CoV-2 invades by binding to angiotensin-converting enzyme 2 (ACE2) receptors presented on the surface of human cells. Interestingly, these receptors are present not only in the respiratory system, but also in cardiovascular system, causing direct damage to the virus. The main pathology of STEMI, however, is due to severe systemic inflammation in patients with COVID-19, contributing to plaque rupture and thrombosis with the release of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin 1 (IL-1), directly and through sympathetic stimulation. On the other hand, this severe inflammation can lead to a rise in the volume of thrombosis in the target vessel and formation of spontaneous thrombosis in nonculprit vessels as well as stent thrombosis, activating the coagulation cascade (Fig 1).

Diagnostic Approach for COVID-19 Patients and STEMI

During the pandemic, the main goal is to diagnose and identify high-risk patients in order to seek emergency treatment. Accordingly, it is demanded that the approaches and diagnostic tools of patients with COVID-19 and STEMI be concise and useful in order to prevent further spread of the disease and reduce the contamination of the medical staff, in particular. As we know, the diagnostic principles of ACS based on the history of patients consist of electrocardiogram (ECG) changes along with cardiac biomarkers, with ECG being the most important diagnostic and treatment decision in patients with suspected STEMI and COVID-19. If the presence of ST-segment elevation along with angina in COVID-19 patients is evident, like other STEMI patients, the diagnosis will be confirmed. Additionally, echocardiography can also be helpful in assessing regional wall motion abnormality in suspected cases. Recent reports have shown an increase in cardiac biomarkers such as troponin from 5% to 25% in patients with COVID-19 who are in intensive care unit. In fact, this increase is due to acute myocardial injury and is associated with a worse prognosis in patients. According to European Association of Percutaneous Cardiovascular Interventions and the Acute Cardiovascular Care Association, a slight increase in troponin (less than 2 or 3 times the ULN) without evidence of myocardial infarction and obvious ECG-based STEMI changes do not require further investigation.
On the other hand, if this marker increases 5 times, further investigation and follow-up will be required. This level of increase is also evident in severe respiratory failure, tachycardia, systemic hypoxemia and shock, with STEMI type 1 being the purpose of diagnosis. With regard to suspicious cases, as mentioned, echocardiography and ECG are very helpful.\textsuperscript{6} CAG is recommended as the final and main diagnostic test, limited to patients with suspected STEMI type 1. In fact, CAG is performed in order to carry out interventional revascularization. However, in Stefanini’s report, 40\% of STEMI patients (11 out of 28 patients) had no evidence of coronary artery disease, and therefore, did not need intervention,\textsuperscript{16} highlighting the need for a correct diagnosis of type 1 MI based on all
clinical and para-clinical findings. During coronary angiography, using methods such as Intravascular Ultrasound and Optical Coherence Tomography can also prove helpful in diagnosing underlying atherosclerotic plaque, even though it is not routinely recommended (Fig 2).21,25

Treatment

As a general principle, the COVID-19 pandemic is not supposed to delay reperfusion therapy in STEMI patients. According to European and American guidelines,26,27 primary PCI should be carried out as the preferred method in the treatment of STEMI and COVID-19 patients in less than 120 minutes after the onset of symptoms. In this regard, it is vital that the health of medical staff be maintained while transferring the patients and performing the procedure. Therefore, all STEMI patients during the COVID-19 pandemic should be considered as suspicious patients and the necessary protections and care principles should be observed to protect the staff. Technically, a 60-minute delay has been experienced for compliance with protective principles and even conducting COVID-19 rapid diagnostic tests in stable patients for primary PCI inclusion (Fig 2). In cases where the patient is hospitalized without catheterization laboratory and rapid transfer is not possible, fibrinolytic therapy is considered an ideal treatment choice.5

Due to the risk of transmission and spread of the disease on the one hand and the unpredictability of cardiovascular events in COVID-19 patients on the other hand, stage PCI is not recommended in these patients, and therefore, complete revascularization in one session can be reasonable.5 In contrast, the study of Hamadeh et al which was performed retrospectively in 4 countries, pointed out that 76% of patients were initially treated by fibrinolytic, 85% of whom had a successful therapeutic response,17 confirming the Chinese recommendation that lytic therapy is preferable in patients with COVID-19 and STEMI.28 However, it is undeniable that the choice of patients and their clinical conditions has certainly had an impact on the outcome of this opposing treatment approach.

As previously mentioned, the predominant finding of CAG in STEMI patients is the presence of huge thrombosis regardless of obstructive plaque, with other vessels being involved at the same time. Due to the high volume of thrombosis and the risk of no-reflow after PCI, aspiration thrombectomy and the use of injectable antiplatelet such as eptifibatide and tirofiban during the procedure or 24-48 hours after the procedure is recommended by most interventionists; however, to achieve thrombolysis in myocardial infarction III flow, their results were different (Fig 2).19-22,25,29,30
Undoubtedly, paying close attention to the care and treatment principles of STEMI and COVID-19 patients after reperfusion therapy is of great importance. Due to lopinavir/ritonavir inhibitory effect on CYP3A4, many drugs, especially novel oral anticoagulants, should be prescribed with great care, on the condition that appropriate indication exists\textsuperscript{31}; However, Kurdi et al prescribed triple therapy for their patient

\textbf{FIG 2.} Diagnostic and therapeutic algorithm of COVID-19 patients and STEMI with coronary artery thrombosis. (Color version of figure is available online.)
due to the concept of high thrombogenicity in patients with COVID-19. Among oral antiplatelets, prasugrel does not interact with COVID-19 therapeutic drugs, but the effect of clopidogrel on concomitant administration of these drugs decreases and ticagrelor increases. Lopinavir/Ritonavir also potentiate the effect of statins, which is recommended to start at the lowest dose if given concomitantly. Hydroxychloroquine can also increase the effect of beta-blockers by reducing heart rate, which requires reducing the possible dose of beta-receptor antagonists in these patients. Administration of aspirin, ACE inhibitors, angiotensin II receptor blockers, and heparin in these patients is unrestricted.

**Stent Thrombosis**

The overall incidence of stent thrombosis in acute and subacute stages as well as late and very late is less than 1%; this statistic, however, has experienced a rise during the COVID-19 pandemic such that the study by Hamadeh et al illustrates a 21% statistic (4 out of 24 STEMI patients under primary PCI) of stent thrombosis. In this regard, published reports indicate the occurrence of all types of stent thrombosis, ranging from acute to very late. As previously mentioned, its mechanism triggers an increase in thrombogenicity due to severe systemic inflammation, followed by activation of coagulation cascade and platelet inhibition in patients with COVID-19. Nevertheless, sufficient attention should be paid to the implantation of previous generations of drug eluting stents (first generation) in late and very late cases, stent malposition and under-expansion and edge dissection in acute and subacute cases as well as clinical risk factors such as chronic renal failure. It is noteworthy that the prescription of the appropriate dual antiplatelet therapy combination is also a subject of debate in patients with COVID-19. Some reports support ticagrelor as a potent and reversible P2Y12 inhibitor, while some others prefer the use of prasugrel owing to its high potency and lack of interaction with COVID-19 therapies.

**Conclusion**

Interpretation of this review suggests that infection with the COVID-19 virus (especially its critical and severe type) with increased thrombogenicity can play a role in the development of acute coronary syndromes, especially STEMI. Surprisingly, CAG of these patients shows large thrombosis as well as simultaneous involvement of several vessels, demanding prompt diagnosis besides timely and appropriate treatment such as primary PCI. Inevitably, paying attention to effective anticoagulant and antiplatelet drug therapy...
before, during and after reperfusion therapy is also a prominent principle in proceeding with the treatment process.

As a new concept, anticoagulant prophylaxis in hospitalized COVID-19 subjects, especially critically ill patients admitted to ICU can reduce thrombosis formation in venous and arterial systems.\textsuperscript{38-40} Finally, large-scale multicenter studies using retrospective and prospective analysis can provide a more appropriate interpretation of the prevalence of coronary artery thrombosis and STEMI in COVID-19 patients, giving us the chance to provide an appropriate therapeutic approach, especially in a long-term follow-up.

\section*{Author Contribution}

M K-A: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review and Editing, Supervision.

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