Myocardial infarction in COVID-19 era

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Abstract

A lot of people were affected with COVID-19, and it has an obvious effect on the heart. There are many cardiovascular complications of corona virus disease. Myocardial infarction is one of the diseases that can be caused by this virus and it is common among those patients. As well as, echocardiographic changes are found in COVID-19 patients like ST elevation that may resemble that of MI. However, the incidence of MI decreased during this pandemic due to many causes including the fear of the patients from catching the infection from the hospitals. In addition to that, there are many mechanisms that can lead to MI in those patients, including cytokine storm. Elevated cardiac troponin in COVID-19 patients may indicate type 2 MI or type 1 but it has a prognostic value. The management didn't change a lot during the pandemic in comparison to before it, however personal protective equipment is very important to protect the medical stuff from the virus.

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INTRODUCTION

Millions of people all over the world have been infected by Coronavirus disease 2019 (COVID-19)(Center., 2020).This virus mainly affects the respiratory system. However, the cardiovascular system can be also disrupted(Shaobo Shi et al., 2020; D. Wang et al., 2020; F. Zhou et al., 2020).

This novel virus can affect the cardiovascular system in both ways: direct and indirect(Tortorici & Veessler, 2019; Xia et al., 2020).These complications are not only common, but also have a bad prognostic value(Xia et al., 2020).

During the pandemic, the rate of admission because of acute myocardial infarction was clearly decreased. Myocardial infarction is one of the most severe extra-pulmonary complication which affects cardiac patients as well as people who carry risk factors of cardiac diseases (De Rosa et al., 2020).

ST-elevation is a common finding in patient with COVID-19 due to either obstructive or non-obstructive causes. It can also happen even on top of normal coronary angiography(Bangalore et al., 2020; Inciardi et al., 2020).The morbidities and the mortalities clearly increased in cardiac patients with COVID-19 infection(Inciardi et al., 2020).

Aim of work

The aim of this work is to make a summary about the present information of COVID-19, giving an attention on the relation between the

coronavirus disease 2019 and the CV (cardiovascular) system.

The virus

COVID-19 is caused by SARS-CoV-2, which is nearly like the SARS-CoV virus(Atri et al., 2020). Its transmission was thought to be from bats that act as a natural reservoir through an intermediate animal host(Atri et al., 2020).Body cells are invaded by this virus through the binding of spike (S) glycoprotein of the virus to ACE2 (angiotensin-converting enzyme 2) receptors(Hoffmann, Kleine-Weber, Krüger, et al., 2020).

Since the Spanish flu of 1918, this outbreak has the highest mortality rate(F. Zhou et al., 2020).Patients with cardiovascular (CV) problems are infected more with coronavirus and the disease in those individuals is more critical. The impact on the heart is by direct and indirect ways, as well as it can interact with CV drugs.Furthermore,cardiac care for the people who are not COVID positive is affected due to the broad impacts of the outbreak on health services (F. Zhou et al., 2020).

Transmission is by self-contamination of the eyes, nose, or mouth after touching infected objects or inhaling droplets from a patient and it also can be transmitted from carriers (those who have no symptoms)(Prevention., 2020).

There are many phases in the coronavirus disease course (Siddiqi & Mehra, 2020).Starting with just constitutional manifestations, and the most characteristics are fever and cough. In the next phase, there are direct viral cytotoxic effects,

especially in the respiratory tract, resulting in respiratory failure and as a consequence acute respiratory distress syndrome (ARDS). The last one is suspected to be due to a hyperinflammatory response to the viral particles resulting in effects all over the body systems, including the CV system (Siddiqi & Mehra, 2020).

Cardiovascular complications of coronavirus disease

1. Acute cardiac injury

It is expressed by high troponin, ECG (echocardiography) changes, or myocardial dysfunction, and it is common in some groups of individuals with coronavirus disease 2019 in hospitals (S Shi et al., 2020).

It is reported that high-sensitivity cardiac troponin I (hsTnI) is more in patients who did not survive than in survivors (Guo, Fan, & Chen, 2020). As well as, there was a pattern of rising high-sensitivity cardiac troponin I in nonsurvivors at day 13 from the beginning of the disease, while it stayed normal in survivors. This proved that the etiology of the injury in acute coronary syndrome (ACS) is acute inflammatory condition (T Guo et al., 2020).

In addition to that, there was a direct proportion between the mortality rate and the amount of troponin increase (T Guo et al., 2020). The

mortality rate was 6 times more in people with elevated troponin than those without (T Guo et al., 2020). As well as, cardiac patients with high troponin had higher mortality, on the other hand, those with normal levels had a better outcome, although still more than individuals without heart diseases or increased troponin (T Guo et al., 2020).

AMI (acute myocardial infarction) may be a significant indicator of illness seriousness and poor outcome in coronavirus disease 2019. Despite that, the mechanisms of this are not clear and they are mostly due to many causes (Figure 1). Plausible etiologies to acute cardiac injury in coronavirus patients include (1) sudden changes in the demand and supply of the myocardium due to increased heart rate, decreased blood pressure, and low oxygen level in blood leading to type 2 MI; (2) ACS; (3) microvascular dysfunction due to diffuse microthrombi or vascular injury; (4) stress-related cardiomyopathy; (5) nonischemic myocardial injury due to a cytokine storm; or (6) direct viral cardiomyocyte toxicity and myocarditis (Atri et al., 2020) (figure 1).

Figure 1: Mechanisms of AMI related to coronavirus disease 2019. (Atri et al., 2020)

2. Myocarditis and pericarditis

They are common CV complications of coronavirus disease 2019 (Inciardi et al., 2020).

3. Heart failure and cardiogenic shock

They are significant causes of death in this viral disease. Approximately one third of mortalities was due to respiratory and heart failure, while only 7% was due to heart failure alone (Ruan, Yang, Wang, Jiang, & Song, 2020). Myocarditis is thought to be the cause of the heart failure, and it is considered that inflammatory condition and cytokine storm are the main mediators of heart failure in coronavirus patients (Siddiqi & Mehra, 2020). That is due to the significantly increased inflammatory markers in those with serious coronavirus disease 2019 (F. Zhou et al., 2020).

4. Thrombosis and venous thromboembolic disease

Doctors are concerned recently about thromboembolism in coronavirus disease 2019. It is reasonable that COVID-19 infection also increases venous thromboembolism probability, this is due to the alterations seen in the

coagulation profiles of people admitted to the hospital with coronavirus disease 2019 with significant high D-dimer (D. Wang et al., 2020; F. Zhou et al., 2020).

Patients who did not survive had an obvious increase in D-dimer during the course of the illness (F. Zhou et al., 2020). On admission, they had high D-dimer and FDPs (fibrin degradation products), lately, most of them had disseminated intravascular coagulation (DIC) (Tang, Li, Wang, & Sun, 2020).

Moreover, antiphospholipid antibodies were reported to be present and also multiple cerebral infarctions (Zhang et al., 2020).

Thus, prophylaxis against venous thromboembolism should be given to all coronavirus patients, as well as they should take anticoagulants for already formed thromboembolisms (Schünemann et al., 2018).

5. Arrhythmias

Less than one fifth of people with coronavirus had arrhythmias, specifically supraventricular tachycardia and it is more prevalent in intensive care unit (ICU) (D. Wang et al., 2020). On the

other hand, patients with high blood levels of cardiac troponin had more commonly severe arrhythmias like ventricular tachycardia and ventricular fibrillation (T Guo et al., 2020).

Echocardiographic findings in COVID-19 patients

Diffuse or focal ST elevation may simulate ST elevation myocardial infarction with no

abnormality in the angiography, and this can indicate inflammation of the myopericardium (Nicola Gaibazzi, Martini, & Mattioli, 1990). Wide varieties of ST segment elevation can be seen in COVID-19 patients and it may be due to myocardial infarction or not (Bangalore et al., 2020) (figure 2 and 3).

Figure 2: ST elevation but not due to an actual myocardial infarction in a coronavirus patient. (Nicola Gaibazzi et al., 1990)

Figure 3: an actual inferior ST elevation myocardial infarction in a patient with coronavirus disease 2019. (Nicola Gaibazzi et al., 1990)

Incidence of myocardial infarction with COVID-19

During this outbreak in Italy, the number of hospitalized patients due to acute myocardial infarction showed a dramatic decline. Indeed, admitted patients for acute myocardial infarction

in the pandemic in comparison to the same time of the last year were halved (De Rosa et al., 2020) (figure 4).

Figure 4: Admissions for AMI during the pandemic. (De Rosa et al., 2020)

This is precipitated by many etiologies. First, patients were afraid of catching the infection from the hospitals thus they decrease their visits to EMS (emergency medical services), especially after the media declared that there is lack of PPE (personal protective equipment) and as a result of that, the novel virus affected many patients as well as many staff members (Indolfi & Spaccarotella, 2020).

Another thesis is related to the focus of the medical system on the pandemic, so most of the hospital resources and members were busy managing it. In line with that, the decrease in hospitalization of ST elevation myocardial infarction was less than that of non ST elevation myocardial infarction (Indolfi & Spaccarotella, 2020).

As well, acute CV diseases incidence is truly reduced and this is due to low physical stress during the quarantine, particularly at the

start of social gathering, so this is another cause of less AMI admissions (C. K. Tam CF, Lam S, et al., 2020 Apr;).

Also, it is pointed out that the duration from FMC (first medical contact) to coronary revascularization was largely increased in individuals with ST elevation myocardial infarction (STEMI). This is so essential as primary Percutaneous coronary intervention (PPCI) and reperfusion medications are important, but not enough: therefore efficient care pathway in order to facilitate the steps for those patients is very important (Stehli J, 2019).

In that regard, there is a major rise in case fatalities and complications detected in this outbreak (De Rosa et al., 2020) (figure 5). Thus, approximately 50% of these patients do not arrive at the hospital, thus deaths and heart failure due to acute myocardial infarction will be considerably more (Cosentino N, 2020).

Figure 5: Case fatality rate for AMI. (De Rosa et al., 2020)

Impact of COVID-19 pandemic on patients presenting with STEMI

During the pandemic, the duration between symptoms presentation and first medical contact was greatly delayed compared to pre-COVID

era. The cardiac troponin-1 (cTn-1) levels on admission were also remarkably higher in the COVID era versus before it (Abdelaziz HK).

The prognosis of ST elevation myocardial infarction (STEMI) depends mainly on the

duration of ischemia, and to decrease the mortality and morbidity, we should manage early(De Luca G).

The duration between symptoms presentation and FMC during the pandemic is remarkably delayed, and this decreases the benefits of primary percutaneous intervention (PCI) in individuals with ST elevation myocardial infarction(Abdelaziz HK).

The obvious increase of cardiac troponin I (ctn-I) level in comparison to the same duration in the previous year is mostly a result of late symptoms and long ischemia duration(Abdelaziz HK). As well as these will lead to more newly diagnosed heart failure patients and deaths so this is another class of indirect complications of the virus (Abdelaziz HK).

Also, evaluation of STEMI individuals after arriving the hospitals is delayed and this is due to many etiologies. To begin with, generalized infection of the surrounding environment can be caused through positive pressure ventilation that is present inside the catheterization rooms(C. K. Tam CF, Lam S, et al., 2020).

We should be so cautious prior to moving the patients to the catheterization laboratories, through taking detailed history including travelling, contacting COVID positive patients and symptoms, as well as X-ray to the chest should be done. In spite of that, this may lead to more delay in managing those patients (C. K. Tam CF, Lam S, et al., 2020).

Proper postintervention sterilization of everything used for catheterization is very

essential, however this may lead to more delay(Driggin E, 2020).

Elective operations including CABG (coronary artery bypass graft) are being reduced or even cancelled by many hospitals(Welt FGP, 2020), but this may lead to low quality of life as these individuals have symptoms and severe illness (Welt FGP, 2020).

Despite that PPCI is the gold-standard therapy for STEMI patients, (Ibanez B, 2018)thrombolytic therapy (TT) has been recommended as the main reperfusion strategy in patients presenting with STEMI during the Coronavirus Disease 2019 (COVID-19) pandemic by many international statement (D. Wang et al., 2020). Patient-physician confrontation during PPCI has been cited as a significant route of infection transmission, and the high rate of transmission from asymptomatic carriers underscores the significance of avoiding unnecessary procedures(D. Wang et al., 2020).

Moreover, medications for coronavirus interact with famous cardiac ones(Driggin E, 2020). Antivirals can interact with anticoagulation drugs, antiplatelet drugs, statins, and antiarrhythmics.

Chloroquine/hydroxychloroquine interferes with β -blockers and antiarrhythmics (Driggin E, 2020), as bradycardia has been reported with hydroxychloroquine and may be aggravated with beta-blockers (Talasaz et al., 2020).

Regarding antiplatelets, Lopinavir is an antiviral drug used for this novel virus; it can increase the risk of bleeding with ticagrelor, as a

consequence, it is contraindicated in patients receiving lopinavir (Talasaz et al., 2020). In patients without coagulopathy and bleeding risk, we can use prasugrel with lopinavir (Bikdeli et al., 2020).

For anticoagulants, low molecular weight heparin (LMWH) may have more merits than unfractionated heparin (UFH) in patients suffering from coagulopathy (Tang, Bai, et al., 2020). If the cardiologist postpones angiography, LMWH can be used as the drug of

choice in those receiving fibrinolytic therapy (Wong et al., 2019).

Mechanisms of myocardial injury in COVID-19

This great effect on the cardiovascular system is by multiple mechanisms including direct myocardial damage, systemic inflammatory response, hypoxia, right heart strain secondary to ARDS and lung injury, and plaque rupture secondary to inflammation (Bandyopadhyay et al., 2020) (figure 6).

Figure 6: mechanisms of myocardial injury due to coronavirus disease-2019 (Wei, Qian, Huang, & Geng, 2020).

1. Direct myocardial injury

Direct myocardial injury—SARS-CoV-2 viral invasion of cardiomyocytes is thought to occur by binding to ACE2, that can result in alteration of its signaling pathways, leading to acute myocardial and lung injury (Bansal, 2020).

Host cells are invaded by SARS-CoV-2 through S protein binding to ACE2 (Hoffmann, Kleine-Weber, Schroeder, et al., 2020). There is protein on the cell membrane called type II transmembrane serine proteases, its role is to cut S protein and expose the receptor-binding part in

order to bind with ACE2. When S protein binds to angiotensin converting enzyme 2, endocytosis of virus particles occurs (Li, Li, Farzan, & Harrison, 2005) and may result in down-regulation of ACE2 expression in cardiomyocytes, and the over-activation of renin angiotensin system.

An autopsy supports that theory by showing the presence of the virus in the cardiomyocytes associated with significant down-regulation of ACE2 expression (Oudit et al., 2009).

2. Hypoxia and ischemic injury

Inflammation and dysfunction of the lungs caused by the virus decreases the oxygen–blood exchange, as a result of that, more hypoxemia, low blood pressure and septic shock may occur (Guan et al., 2019). Thus vital organs like the heart may not be supplied with sufficient blood. At the same time, oxygen needed by the heart is more because of fever that leads to higher metabolic rate and as a consequence inflammation increases and the balance between supplied oxygen and that consumed is disturbed (Heusch, 2016).

As the virus is progressing, this imbalance becomes more and more due to several etiologies including metabolic acidosis, fluid or electrolyte disorder, and impairment of the neuro-humoral system (Tavazzi et al., 2020). Therefore, myocardial affection in coronavirus individuals can be caused by indirect ways particularly in patients with already diagnosed heart diseases (Tao Guo et al., 2020).

3. Abnormal coagulation and microcirculatory disturbance

Vascular endothelium can be attacked by COVID-19 in a direct manner, that leads to high levels of expressed ACE2, resulting in coagulation abnormalities and disturbed microcirculation (Hamming et al., 2004). In addition, disturbed blood flow in the microvasculature may lead to focal ischemic changes and then AMI (Sugiura et al., 1977). A new study has proved that the incidence of myocardial injury is more in those with DIC

(disseminated intravascular coagulopathy) (Y. Wang et al., 2020).

4. Cytokine storm

It means massive secretion of cytokines in response to virus invasion and it contributes in a major way to the pathogenesis of myocardial injury. Pro-inflammatory cytokines are significantly high in patients with coronavirus disease 2019 and this indicates disease progression (Huang et al., 2020).

It is reported that Th2 anti-inflammatory cytokines, including IL-4 and IL-10, are elevated, and they are an indicator of disease seriousness (Chen et al., 2020). Those with no symptoms had less cytokines than those with symptoms, suggesting the pathogenic role of cytokines (Long et al., 2020).

IL-6 is considered the major inflammatory cytokine and it is expressed in a very high levels in those with critical situations and suspected bad outcomes (Chen et al., 2020). It does not only amplify the cytokine storm by stimulating the production of other pro-inflammatory cytokines but it encourages as well the vascular leakage and interstitial oedema (Tanaka, Narazaki, & Kishimoto, 2016).

Moreover, high troponin levels is significantly associated with elevated IL-6 in patients with coronavirus admitted to the hospitals (Wu et al., 2020). All of this indicates that the main contributor in cytokine storm to develop myocardial injury is IL-6 (Wei et al., 2020).

Controversies regarding ACE inhibitors/angiotensin receptor blockers

ACE2 is a receptor for COVID-19, physicians are concerned about the drugs that leads to its upregulation like ACE inhibitors and ARBs (angiotensin receptor blockers) which are used for hypertension treatment, as it may have a negative impact (Kuster et al., 2020). It was proposed that this increase in ACE2 expression supports the greater COVID-19 severity (Bozkurt, Kovacs, & Harrington, 2020), however, bad outcomes among patients were not linked to the use of these drugs (56). In addition to that, these drugs have no effect on the COVID-19 infection susceptibility as it was found that there is no interaction between RAS (renin angiotensin system) blocking drugs and test positivity (Mancia, Rea, Ludergrani, Apolone, & Corrao, 2020).

We have to discuss some major things. Starting with the debatable impact of RAS inhibitors on ACE2 (Vaduganathan et al., 2020). ACE and ACE2 are structurally similar but they differ in their targets. ACE changes angiotensin I to angiotensin II, while ACE2 breaks angiotensin II to angiotensin(P. Zhou et al., 2020).

Downstreaming of angiotensin II caused by ACEIs and ARBs is due to prevention of angiotensin I to be converted to angiotensin II by ACEIs, and blockage of angiotensin II receptor type 1 by ARBs (Vaduganathan et al., 2020). So, neither one of these medications has a direct impact on ACE2. Despite that, treatment

with ACEIs or ARBs in animal studies showed a rise in the expression of ACE2 (Ferrario et al., 2005).

In clinical studies, patients who use captopril (ACEI) for long duration (Luque, 1996) or olmesartan (ARB) (Furuhashi et al., 2015) had elevated angiotensin blood levels (Connors & Levy, 2020) or urinary levels of ACE2, that indicates highly active ACE2. On the contrary, patients with heart failure (Epelman et al., 2009), aortic stenosis (Ramchand et al., 2020), atrial fibrillation (Walters et al., 2017) or coronary artery diseases (CAD) (Ramchand, Patel, Srivastava, Farouque, & Burrell, 2018) do not have ACE2 upregulation despite using RAS inhibitors.

Such conflicting results are mostly due to the indirect effects of ACEIs or ARBs on ACE2, that rely on several conditions like ACE2 baseline expression levels, doses and treatment duration. Second, no direct proof showed that upregulation of ACE2 has an effect on susceptibility to viral infection (Vaduganathan et al., 2020).

However, it is hardly recommended that treatment for hypertension with ACEIs and ARBs should be continued as there is no proved evidence to discontinue them during the pandemic (de Simone, 2020).

Troponin elevation suggesting myocardial infarction in patients with COVID-19

Those with previous CAD or even risk factors for atherosclerosis have more susceptibility of developing acute coronary syndrome (ACS)

with any acute infection (Cheng et al., 2020) or inflammation. This might be as a consequence of disturbed balance between oxygen supply and demand (Smeeth et al., 2004).

As well as, low oxygen in the blood may result in massive intracellular calcium and as a consequence death of cardiomyocytes (Zheng, Ma, Zhang, & Xie, 2020). Type 2 MI can be caused due to CAD or even without. However, increased blood levels of troponin in coronavirus patients may indicate type 2 myocardial infarction as the pre-existing stable CAD is aggravated by the infection. Type 1 myocardial infarction can also be caused by this virus through plaque rupture with thrombus formation (Thygesen et al., 2019).

High troponin is considered as a good prognostic factor in coronavirus patients. High troponin at the beginning is associated with more severe disease (Oudkerk et al., 2020) and more ICU admissions. In addition to that, stratification of the risk of death is according to the level of troponin elevation and pre-existing CVD (S Shi et al., 2020).

Management

a) Definite ST elevated myocardial infarction

The main line of treatment for STEMI patients within 90 minutes from FMC is primary percutaneous coronary intervention, and it should remain the standard during the pandemic (Mahmud et al., 2020).

Compared to fibrinolytics, Primary PCI is better for setting normal blood flow in the coronaries as well as it has less bleeding

probability (Mahmud et al., 2020). Moreover, more than half of the patients need PCI after fibrinolysis, as a result of that, longer hospital stay will be needed thus free beds for coronavirus patients will be limited (Mahmud et al., 2020).

As well as, STEMI-mimickers are common in COVID-19 including focal myocarditis or stress cardiomyopathy (Madjid, Safavi-Naeini, Solomon, & Vardeny, 2020). Those patients did not get any benefits from fibrinolysis but it can increase the risk of bleeding and they may need catheterization for diagnosis. If staff and PPE are not available as well as catheterization laboratories, a fibrinolysis first approach should be considered (Mahmud et al., 2020).

These patients with STEMI should be evaluated first in the emergency department prior to catheterization to make sure that appropriate risks are assessed. Face mask is required for all patients to decrease the risk of contamination of the surrounding and infection spread. PPE should be available to the people who will attend the procedure especially an N95 respiratory mask (Mahmud et al., 2020). In addition, if there is lung dysfunction, intubation should be achieved before arriving to the catheterization lab (Mahmud et al., 2020).

On the other hand, FT (fibrinolytic therapy) is recommended in China over PPCI for STEMI (Daniels, Cohen, Bavry, & Kumbhani, 2020). Outcomes of FT in comparison to PPCI were similar regarding death, shock, heart failure, or reinfarction, but intracranial

hemorrhage was higher with FT. If delays in PPCI are unavoidable, a pharmacoinvasive approach is not worse than PPCI (Daniels et al., 2020).

Timely PPCI depends mainly on systems of care, not just individual operators. PPCI treatment delays in the pandemic arise, even among those who are free from the virus. Thus, fibrinolysis in the emergency department may lessen systems-based delays. A door-to-needle time of 30 minutes may have a better outcome than a door-to-balloon time of 90 minutes as early reperfusion is more important than the mode of reperfusion (Daniels et al., 2020).

b) Possible ST elevated myocardial infarction
If the diagnosis is not sure due to atypical presentation, these patients should be evaluated in the ED (Mahmud et al., 2020). This evaluation relies on two items: (a) stratifying the risk for coronavirus disease 2019 and (b) more evaluation of the diagnosis especially for CAD. Despite that, hemodynamic stable patients might still require an invasive catheterization to reach a conclusive diagnosis (Mahmud et al., 2020).

c) Patients with non-STEMI
Coronavirus positive individuals with Non-STEMI are managed medically and invasive procedures like PCI are only limited to high risk patients (Mehta et al., 2009). If there are no risk factors, medical treatment is used till stabilization of the patient then outpatient follow up and coronary angiography at a later time after resolving of the infection (Mahmud et al., 2020).

Conclusion

Coronavirus disease 2019 has a widespread impact on all body systems, not only the respiratory, including the CV system. Cardiac injury may occur through possible ischemic and nonischemic mechanisms. The spike protein and ACE2 relationship is likely to have a major role in the pathogenesis of this illness, especially in CV symptoms.

CV biomarkers should be monitored essentially, and we should diagnose early, and try to prevent myocardial dysfunction by this novel virus.

During this pandemic, the main line of treatment of ST-elevation myocardial infarction is primary PCI while for non ST-elevation myocardial infarction patients who are affected by coronavirus are mainly managed with an initial medical treatment.

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