Coronary Thrombosis in COVID-19 Patients

Prevalence, Mechanisms, Diagnosis, Treatment, and Precautions

Introduction

Corona virus disease-2019 (COVID-19) is a new mysterious viral infection that is rapidly spreading worldwide caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and has deleterious impacts on global health and economy [**1] [2]**.

Egyptian ministry of health had announced the first case in the country at Cairo International Airport involving a Chinese citizen on 14 February 2020 **[3]**.

The mode of infection of COVID-19 is thought to be direct entry of the SARS-CoV-2 virus into cells via the human angiotensin-converting enzyme-2 (ACE2) receptor, which is expressed predominantly in the lungs but also throughout the cardiovascular system **[1]**.

Symptoms range from asymptomatic or mild constitutional symptoms to pneumonia, sepsis and sometimes severe acute respiratory distress syndrome (ARDS) necessitating hospitalization and intensive care unit (ICU) admission **[4]**.

However, it is believed that the worst prognosis would be for a patient with combined COVID-19 and STEMI **[2]**.

There are increasing reports of cardiac involvement of COVID-19, ranging from myocyte biomarker elevation and electrocardiographic abnormalities, to myocardial dysfunction, and arrhythmias **[5]**.

Hypercoagulability has been identified to play a key role determining prognosis in patients with COVID-19 **[4]**.

Incidence of thromboembolic disease is reported to be high in SARS-CoV2 disease and is seen in a multitude of organ systems ranging from cutaneous thrombosis to pulmonary embolism, stroke or coronary thrombosis sometimes with catastrophic outcomes **[4].**

Coronary thrombosis is one of causes of sudden death in covid-19 **[6]**.

Prevalence:

No clear data regarding prevalence of coronary thrombosis in covid-19 patients but many case reports documented coronary thrombosis with heavy thrombus burden in covid-19 positive patients presented with acute myocardial infarction in Egypt, Germany, USA and other countries **[4]**.

The overall prevalence of acute myocardial injury among covid-19 patients ranged from 5% to 38% depending on the criteria used, the overall crude prevalence of acute myocardial injury was 21.4%. Using meta-analytic approach, the overall weighted pooled prevalence estimate of acute myocardial injury was found to be 20% **[7]**.

Lodigiani and his colleagues stated that the rate of acute myocardial infarction among 388 patients admitted with covid-19 was 1.1% **[8]**.

Mechanisms:

Thrombo-inflammation and endothelial dysfunction play an essential role in the pathogenesis of the disease **[4]**.

Up to 50% of the patients admitted in ICUs with COVID-19 pneumonia develop thrombotic events **[6]**.

Antithrombin values were lower while values of D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen (FIB) in all SARS-CoV-2 cases were substantially higher than those in healthy controls **[9]**.

The exact mechanism of coronary thrombus formation in COVID-19 is not known. Elevated inflammatory cytokines are present in patients with COVID-19. Pro-inflammatory cytokines activate the coagulation cascade and inhibit fibrinolysis. Tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFNγ) and interleukin 1 (IL-1) predominantly cause a pro-coagulant state in COVID-19. This pro-coagulant state can lead to leukocyte migration and adhesion, platelet activation and adhesion, and endothelial dysfunction resulting in thrombus formation **[10]**.

Figure **(1)** shows proposed cytokine cascade in SARS-CoV-2 leading to thrombus formation **[10].**

Another possible mechanism of coronary thrombosis is production of Neutrophil extracellular traps (NETs) which are extracellular webs of chromatin, microbecidal proteins, and oxidant enzymes released by neutrophils to contain infections. However, when not properly regulated, NETs have the potential to propagate inflammation and microvascular thrombosis **[11]**.

NETS in COVID-19 patients was believed to be the culprit behind the propagation of inflammation, cytokine release and thrombosis **[2].**

Also, NETS causes platelet aggregation leading to enhanced coagulopathy and massive coronary thrombosis **[2].**

The role of NETS was raised after observation of high levels of NETS' highly specific markers (as cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 [Cit-H3]) in the sera of COVID-19 patients, also serum samples from patients with COVID-19 robustly triggered healthy neutrophils to undergo NETosis **[2] [11].**

Activation of Renin-Angiotensin System (RAS) may contribute in coronary thrombosis in covid-19 patients. Angiotensin converting enzyme-2 (ACE2) is predominantly expressed by epithelial cells of the lung, intestine, kidney, heart, and blood vessels. It is recognized as a protective molecule against renal, cardiac, hepatic, and respiratory diseases in the context of negative regulation of the RAS. While ACE cleaves angiotensin I to angiotensin II and leads to vasoconstrictive, pro-inflammatory, and pro-oxidative effects through the angiotensin II receptor type 1 (AT-1) receptor **(figure 2)**, ACE2 leads to anti-inflammatory, anti-oxidative and vasodilatory effects through the angiotensin 1-9-Mas receptor complex. ACE2 is now also recognized as a functional receptor for SARS-CoV-2 as the virus uses the ACE2 for entry into target cells. The virus-ACE2 recognition is too efficient and the SARS-CoV-2 spike protein has a strong binding affinity to human ACE2. This virus uses ACE2 not only for its cellular entry to the host cell but also downregulates ACE2 expression, contributing to the pathogenesis of severe acute respiratory syndrome (SARS) **figure (3) [12]**.

The protective effect of ACE2 in lung is well defined, and therefore down regulation of ACE2 due to viral binding to this receptor plays a key role in acute lung injury and acute respiratory distress syndrome **[7]**. Also the

wide distribution pattern of ACE2 expression explains the multiple organ dysfunction with COVID-19 patients **[12]**.

Case reports indicate that the inflammatory/prothrombotic state associated with SARS-CoV-2 infection is related not only to thromboembolic disease or the microvascular territory, but may also entail a higher risk of atherosclerotic plaque rupture in the arterial system, as previously reported with other respiratory viruses **[13]**.

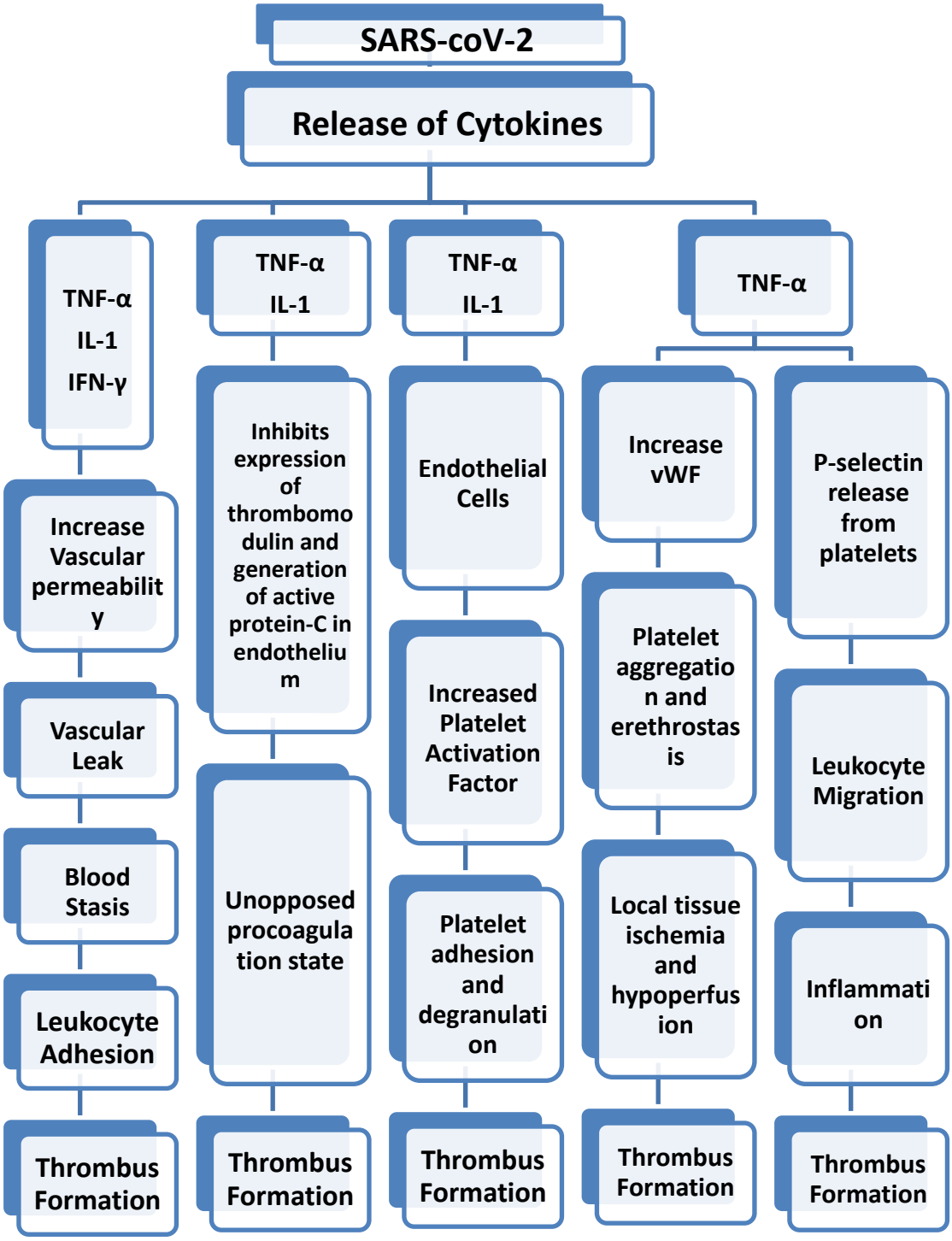

Figure (1) Proposed cytokine cascade in SARS-CoV-2 leading to thrombus formation [10]

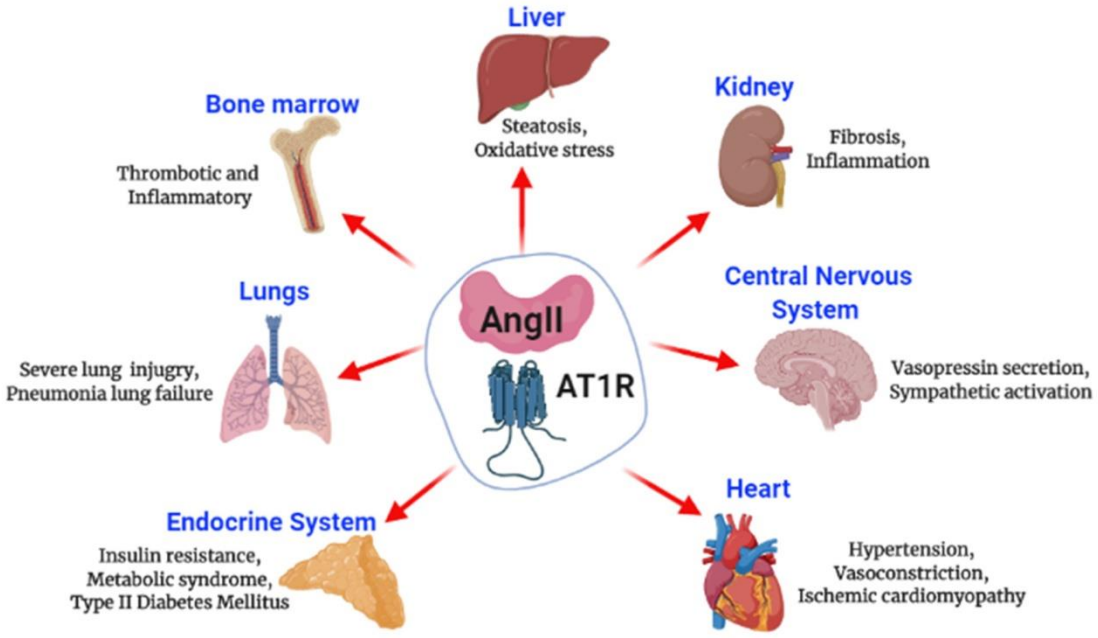

Figure (2) Deleterious effect of Angiotensin II on combination with angitensin 1 receptor (AT1R) [12]

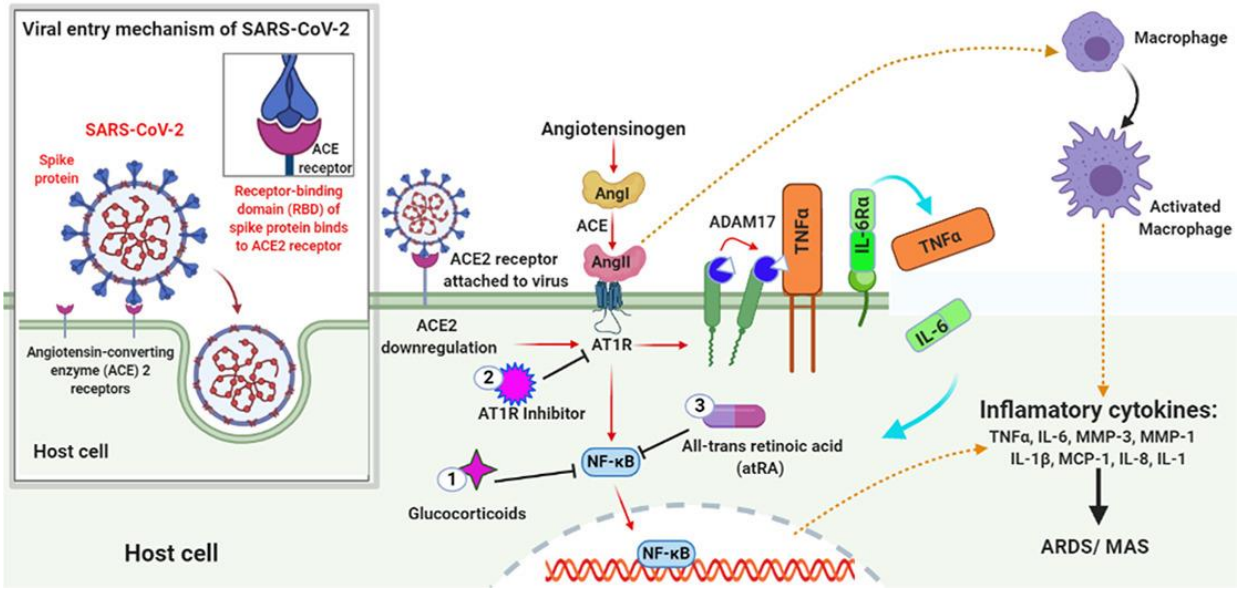

Figure (3) Illustration of ACE2 Downregulation in COVID-19 patient and appearance of macrophage activation syndrome (MAS) [12]

Diagnosis

Diagnosis of coronary thrombosis in COVID-19 patients may be little bit challenging. It may affect young patients without risk factors of coronary artery disease **[10]**. Patients with COVID-19 may show ST-segment elevation may be diffuse or regional, mimicking a STEMI; also elevated cardiac biomarkers were reported in those patients without an angiographic culprit lesion. These changes may be indicative of myopericardial inflammation or apical ballooning and the presence of reciprocal ECG changes appear to be a key for differentiation together with echocardiography and coronary angiography **[14] [15]**.

Treatment:

The acute treatment of STEMI is similar to that in non-COVID-19 patients and should be in line with the current guidelines for Non-COVID-19 patients with consideration of the safety of health care professionals **[16]**. It includes prompt recognition of symptoms, rapid laboratory analysis, including ECG, cardiac troponins, bed side echocardiography, and primary percutaneous coronary intervention (PPCI) **[10]**.

During the COVID-19 pandemic, PPCI remains the standard of care for STEMI patients at PCI capable hospitals when it can be provided in a timely manner, with an expert team outfitted with Personal Protective Equipments (PPE) in a dedicated cath-lab room **[17]**.

The main difference is related to a possible transfer delay secondary to COVID-19 for patients presenting to a non-PCI capable hospital. **[10]**.

PPCI is the first choice in COVID-19 patients presented with STEMI over fibrinolytic therapy which is unlikely to be able to deal with massive coronary thrombi documented in many case reports **[2]**.

Many case reports of covid-19 patients showed failed thrombolytic therapy and recurrent stent thrombosis with high fatality **[18]**.

The potent new generation of P2Y12 inhibitors such as prasugrel should be preferred **[2]**. There have been reports of interactions (related to

CYP3A4) between some of the antiviral drugs used, particularly lopinavir/ritonavir and darunavir/cobicistat, and clopidogrel and ticagrelor. These interactions decrease the formation of the active metabolite of clopidogrel and thus decrease its antiplatelet efficacy, whereas they increase the concentrations of ticagrelor and thus increase its antiplatelet efficacy. For this reason, the use of prasugrel has been proposed in these patients, although with qualifications **[19]**.

Sub-acute stent thrombosis was reported in patient discharged on clopidogrel and aspirin and the patient presented with acute inferior STEMI 5 days after PCI to RCA and LAD for NSTEMI **[20]**.

Upstream administration of GP IIb/IIIa inhibitors could be considered in every patient with STEMI and suspected or proved COVID-19 infection planned for primary PCI in an attempt to achieve favorable conditions at the time of intervention for PPCI **[2]**.

It is recommend continuing GP IIb/IIIa inhibitors infusion post-primary PCI to prevent acute stent thrombosis and get favorable outcomes after stent implantation **[2]**. Some case reports recommend additional use of therapeutic dose of heparin simultaneously for 24 hours **[10]**.

Thrombus aspiration may be used to decrease thrombus burden but it failed to restore adequate TIMI flow in many case reports **[10]**.

Although primary angioplasty is the preferred reperfusion strategy in patients with ST-segment elevation acute myocardial infarction, fibrinolysis can be considered in patients with an estimated time from diagnosis to coronary intervention of more than 120 minutes, in infected patients with poor clinical status that hinders transfer, or in those at low risk of bleeding and with symptom onset less than 3 hours **[19]**.

Statins have direct anti-inflammatory effects beyond their lipid-lowering actions, mediated by inhibition of prenylation of small G proteins or induction of transcription factors such as KLF-2 that promote homeostatic endothelial functions. Non-randomized treatment with statins yielded preliminary retrospective evidence of improved outcomes in COVID-19, as well as reductions in biomarkers of inflammation **[21]**.

Small, non-randomized studies of a recombinant form of the endogenous IL-1 receptor antagonist, anakinra, have furnished sufficient encouragement to merit further definitive investigation. Anakinra blocks both IL-1a and IL-1b, and requires daily dosing. Canakinumab, a selective IL-1b antibody, has a much longer biological half-life than anakinra, rendering it less readily reversible. Several studies investigating canakinumab in COVID-19 are underway **[21]**.

Precaution and protection of health care worker (HCW)

The shortages of PPE during the initial period of the pandemic have been well documented and contributed to the deaths of many HCWs **[5]**.

In a survey by Sharaf et al 2020 which included 30 cath-labs distributed all over Egypt during COVID-19 pandemic, only 63.3% of surveyed centers were well equipped to deal with COVID-19 active patients with the majority of them (60%) using only surgical mask and face shield in patients not suspected to have COVID-19; at the same time, full PPE was worn in only 6.7% of patients **[3]**.

Although cardiac catheterization is typically not an aerosol-generating procedure, the potential need for CPR or intubation exists—especially in acutely ill patients. The use of PPE for the staff including covering for the head, eyes/face, and body and N95 masks appears as a common recommendation in societal consensus documents for patients with documented and those at risk of SARS-CoV-2 **[5]**.

Treatment delays for ACS (particularly STEMI) on the part of patients fearing exposure and on the health care system related to need for more thorough patient evaluation have been noted. Time delays related to staff donning of PPE and room preparation may be present **[5]**.

CPR is a high-risk procedure in patients with COVID-19. Emphasis on aggressive PPE protection and early defibrillation (prior to chest compressions) has been recommended **[5]**.

The following precautions should be considered before cath-lab: Minimize pre- and post-procedure waiting times, use surgical masks in all patients while they wait, questioning of all patients about respiratory

symptoms, fever, and close contacts before entry to the lab, temperature-taking in all patients **[22]**.

Inside cath-lab: Allow only essential staff to enter the lab, keep doors shut at all times, patients should put a surgical mask, prepare drugs before patient entry to the lab. Cath-labs should prepare COVID-19 carts with all potential supplies for other invasive procedures such as intra-aortic balloon pump, pericardiocentesis, ECMO, and temporary venous pacemakers. Avoid leaving the lab with contaminated equipment (e.g., gown, gloves, and mask) to collect material (e.g., stents and catheters) **[22]**.

Conclusion

Management of coronary thrombosis in COVID-19 patients remains a key priority and services must be configured in an adaptable manner to respond to the changing demands in the pandemic. PPCI remains the gold standard to deal with STEMI associated with coronary thrombosis but HCW safety should be taken in consideration.

Points for discussion

- ACE inhibitors/ARBs use with SARS-CoV-2
- COVID-19 and Kawasaki Disease
- Use of Tolicizumab (Actemra) in COVID-19 patients (IL6 inhibitor) according to level of IL6 and procalcitonin
- Pathways of inflammation in COVID19: ACE2, JAK/STAT, Notch pathways

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