

COVID-19: Cardiovascular perspective.

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Introduction

Recently the outbreak of COVID-19 has created a nuisance in the health care system throughout the world. There are multiple early reports covering the cardiovascular perspective of COVID 19. However, there are limited guidelines/protocols addressing the issue. With the emerging pandemic, data is ever-changing and so is our understanding of the cardiovascular implication of COVID-19.

Relation of cardiovascular disease with COVID-19

The current global trend reflects that COVID-19 is a clinically significant disease and has more fatal outcomes in patients with preexisting comorbidities including cardiac diseases. In an initial report of 99 patients published in the Lancet from Wuhan, China, 40% of patients had a history of cardiovascular disease.¹ Another report from China showed that 26% of COVID-19 patients required cardiac intensive care during their hospital stay. The indication of cardiac intensive care admission was arrhythmias in 16.7% and acute coronary syndrome in another 7.2% of those patients.² At least one form of cardiovascular manifestation was seen in 7% of confirmed COVID-19 and 22% of those with seriously ill patients.³ Another study done on 191 admitted patients of COVID-19 showed that hypertension was the most common co-morbidity seen in 30% of patients followed by diabetes and coronary heart disease in 19% and 8% patients respectively.⁴

In contrast, a meta-analysis of 6 different studies on COVID-19 done in china showed that the proportions of hypertension, cardio-cerebrovascular disease, and diabetes in patients with COVID-19 were 17.1%, 16.4%, and 9.7% respectively.⁵ Chest tightness was the first manifestation of the COVID-19 in 10.7% of cases and less than 5% of patients presented with chest pain.⁶ Another study reported that 15.48% of patients manifested abnormal electrocardiograms and cardiac biomarkers. SARS-CoV-2 myocarditis was clinically diagnosed in 4.8% of total patients diagnosed with COVID-19.

Management of Acute coronary syndrome (ACS) patient in the setting of COVID-19

The COVID-19 & AMI committee of Peking Union Medical College Hospital, China designed a recommendation that was published on the European Heart Journal on 31st March 2020 regarding the management of ACS in the setting of COVID-19. They recommend intravenous thrombolysis as the first choice of revascularization therapy in all acute ST-elevation myocardial infarction (STEMI) patients with COVID-19. This recommendation was later endorsed by the American college of cardiology (ACC). Based on this recommendation and considering the fact that most of the cardiac catheterization lab worldwide lack professional protection, any suspected COVID-19 patients with STEMI should undergo the basic investigations to rule out COVID-19 first followed by initiation of intravenous thrombolysis within 30 minutes after ruling out the contraindications. In all diagnosed cases of COVID-19 with STEMI, it is recommended to start intravenous thrombolysis first if there are no contraindications, followed by transfer of patients to designated COVID-19 hospital for further treatment. In all of them strict isolation measures should be started immediately.⁸

The non-ST-elevation myocardial infarction (NSTEMI) patients should be managed by optimal medical treatment after GRACE scoring and intervention therapy can be considered after COVID-19 is ruled out by the expert panel.⁸

Cardiovascular drugs in COVID-19

Angiotensin-converting enzyme 2 (ACE2) is recognized to be a co-receptor for viral entry in COVID-19. Moreover, the use of Angiotensin-converting enzyme inhibitor (ACEI) and Angiotensin II receptor blockers (ARBs) in patients with COVID-19 will increase the expression of ACE which in turn increases the patient susceptibility to viral host cell entry and propagation.⁹ Thus, altered expression of

ACE2 may be in part responsible for disease virulence in the ongoing Covid-19 pandemic.¹⁰ However, it is thought that ACE2 functions as a carboxypeptidase which cannot be inhibited by RAAS blocking drugs like ACEI and ARBs.⁹ Therefore the use and discontinuation of these drugs in the context of COVID-19 are still controversial. The joint statement from the ACC, American Heart Association (AHA) and Heart Failure Society of America (HFSA) was posted online on March 17 and addresses using renin-angiotensin-aldosterone system (RAAS) antagonists in COVID-19.¹¹ The HFSA, ACC, and AHA recommend the continuation of RAAS antagonists for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease.¹¹

A study published on The Lancet-Respiratory medicine revealed that Ibuprofen via an increase in ACE2 will facilitate the infection with COVID-19 especially in hypertensive and diabetic patients.¹² Thus; various concerns on usage of Ibuprofen in COVID-19 patients were hypothesized. However, the World Health Organization (WHO) on 19th March 2020 suggested that there is no enough evidence for it and does not recommend not using ibuprofen in COVID-19. Considering the increased mortality in COVID-19 patients with cardiovascular disease and diabetes mellitus, statin therapy needs to be continued in all the patients among those who are already taking it. Also, few studies suggest that statins may have a beneficial effect in patients with MERS-COV (other coronavirus similar to current 2019n-COV) and hence we can anticipate the benefit of statins in COVID-19 although no large scale studies are done yet to prove it.¹³ Also, the administration of statin has shown to reduce mortality in those with ventilator-associated pneumonia (VAP). However the study population was all patients admitted in critical care unit with a diagnosis of VAP, rather than COVID-19 patients with the diagnosis of VAP.¹⁴ Thus, the use of statins may be considered in COVID-19 patients.

Acute Myocardial injury in COVID-19

The proposed mechanism for acute myocardial injury in the form of myocarditis in patients with COVID-19 is via activation of ACE2 mediated signaling pathways. In addition, cytokine storm, hypoxemia, and respiratory failure are also other mechanisms of myocardial injury. In a preliminary study done in Wuhan, 5 cases of myocarditis were reported in the initial 41 patients diagnosed with COVID-19. Out of these 5 patients, 4 patients were critically ill and required management in the critical care unit. Moreover, among the people who died from COVID-19 reported by the national health commission of China, 11.8% of patients without the preexisting cardiovascular disease had myocardial injury.¹⁵

Catheterization and catheterization laboratory considerations in COVID-19 patients

Emphasis should be given for infection control by providing appropriate PPE to all staff, N95 masks to patients, and limiting the number of catheterization laboratory (cath lab) staff. Intravenous (IV) thrombolysis is preferred in STEMI in patients who are suspected or are suffering from COVID-19. Wherever possible, procedures like intra-aortic balloon pump (IABP) insertion, pericardiocentesis, and temporary pacemaker implantation should be performed bedside instead of cath lab in all suspected and diagnosed cases of COVID-19. Procedures like endotracheal intubation and cardiopulmonary resuscitation (CPR) cause aerosolization and increase the risk of spread of infection, therefore whenever required and feasible intubation should be performed before transferring to the cath lab. Also, alternate diagnosis like type II myocardial infarction (MI), myocarditis, sepsis with positive cardiac biomarkers should

be considered in all patients with diagnosed or suspected COVID-19 before planning for any cath procedures.^{16,17}

Palliative care consideration in the patient with cardiovascular disease with COVID-19

Recent reports suggested that 80% of total COVID-19 deaths in China and the USA were of age more than 60 years and 65 years respectively. Similarly, COVID-19 mortality is highest in 85 years and older (10-27%) followed by 65-84 years (3-11%).¹⁸ More than half of the admitted patients of COVID-19 in Washington had some form of preexisting cardiovascular disease. Thus, palliative care has to be integrated with the standard cardiovascular care while treating critical patients with COVID-19 with or without preexisting cardiac diseases.¹⁹ The basic elements of palliative care for a cardiologist while managing COVID-19 include identifying resources, advance care planning, symptomatic care, pain management, tackling with anxiety, and depression. Similarly, care of dying patients with COVID-19 especially those who are isolated for treatment requires special attention.¹⁹

Role of cardiac biomarkers and Brain Natriuretic Peptide (BNP) in COVID-19

A recent retrospective study done among 191 patients of COVID-19 in China revealed that levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and IL-6 were clearly elevated in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration. Similarly, high sensitivity troponin I increased rapidly from day 16 after the onset of disease whereas lactate dehydrogenase increased for both survivors and non-survivors in the early stage of illness, but decreased from day 13 for survivors. Increased high-sensitivity cardiac troponin I during hospitalization was found in more than half of those who died.⁴

Similarly, another study done in China showed that patients with higher NT-proBNP (above 88.64 pg/mL) level had more risk of in-hospital death. NT-proBNP was presented as an independent risk factor for in-hospital mortality in patients with severe COVID-19.²⁰ On the ground of high frequency of elevated high sensitivity Troponin I and BNP in COVID-19, ACC recommends its testing only if the diagnosis of acute myocardial infarction or heart failure is considered in clinical grounds.²¹

Considerations for protection of patients, Echocardiography service providers, and in Cardiology out-patient clinics

It is a widely accepted fact that cardiac service providers are at high risk of transmission of COVID-19 disease. It is mostly due to exposure to patients with the long incubation period of the disease, decompensation of preexisting cardiac illness, and the potential cardiac complications like myocarditis in patients with COVID-19. American society of echocardiography (ASE) recently published a statement on the Protection of Patients and Echocardiography Service Providers during the 2019 Novel Coronavirus Outbreak. The statement addresses the key elements like whom to image? How to image? Where to image? Review of indications, protection of patients, and service providers. The procedures like transthoracic echocardiograms (TTE), stress echocardiograms, and transesophageal echocardiograms (TEE) should only be performed if they are expected to provide clinical benefit. The urgent and non-elective indications should be identified, and all others should be deferred if such deferral doesn't have an adverse effect on the patient's outcome.

TEEs carries a heightened risk of spread of the SARS-CoV-2

since it may provoke aerosolization of a large amount of virus due to coughing or gagging that may result during the examination and hence should be considered very cautiously. Other diagnostic modalities like CT, MRI can be used as an alternative to TEE for the exclusion of left atrial appendage thrombus prior to cardioversion. Similarly, treadmill or bicycle stress echo tests on patients with COVID-19 may lead to exposure due to deep breathing and/or coughing during exercise. These tests should generally be deferred or converted to pharmacological stress echocardiography.

All Echocardiography procedures (TTE, TEE, and stress tests) should be performed with portable machines in wards, emergency units, bedsides, recovery rooms, and intensive care units instead of echocardiography laboratories to reduce the transmission by decreasing the mobility of patients. In the outpatient setting, patients should be screened for infection according to local protocols and has to be kept in quarantine according to local quarantine protocols. Echocardiographic studies performed on patients with suspected or confirmed COVID-19 should be as focused as necessary to obtain diagnostic views but should also be comprehensive enough to avoid the need to return for additional images. The images can be saved to allow remote interpretive assistance from more experienced echocardiographers. A sonography student or any other novice/inexperienced practitioner should not perform these studies in order to minimize scanning time while obtaining images of the highest possible quality. Imaging should be done as per the standards for the prevention of virus spread. The key elements to be considered include frequent hand washing, use of surgical masks, special masks, gloves, head cover, foot cover, shoe cover, and eyeshield by the provider. Surgical mask for all the diagnosed or suspected COVID-19 patients is a must. Limiting the number of service providers and learners should be considered.

On the other hand it is crucial to consider care of echocardiography equipment as well. Most viricidal disinfectant solutions eliminate SARS-CoV-2. Probes should be adequately cleaned, and wherever possible small size devices that are suitable for disinfection should be considered. TEE probes, chords, and handle should be cleaned followed by immediate transfer to a closed container.^{22,23}

As the initial symptom mimics that of cardiovascular disease in some proportion of COVID-19 patients, cardiology outpatient clinic service providers are at high risk. All cardiologists are required to use proper personal protection like gloves, protection suits, N95 masks, caps, goggles, protective screens, etc. Temperature measurements should precede outpatient clinic visits of patients with adequate social distancing in the waiting area. One doctor, one patient, and one consultation room method should be strictly implemented. Patient, visitors and other medical staffs conducting procedures like electrocardiogram should be properly protected.²⁴

Future Perspective

The global COVID-19 crisis has multiple direct and indirect implications in cardiovascular care throughout the world. It may be quite early to measure the magnitude of its impact on cardiovascular mortality at this point in time. However, the initial data based on multiple studies done globally can be used to anticipate the burden. Moreover, the drugs proposed for treatment of COVID-19 including antivirals, hydroxychloroquine, steroids, biologics and immunosuppressive agents all have some form of cardiovascular side effects and the actual burden will be available from retrospective studies in near future.²⁵

The combination therapy with hydroxychloroquine and azithromycin in patients with COVID-19 is promoted as an eminent treatment and is being used widespread especially in the United States.

These drugs in combination are thought to significantly decrease the viral load and even disappearance of COVID-19. It was supported in a recent open-label non-randomized clinical trial done in France.²⁶ Many other recent clinical studies of drugs like hydroxychloroquine with or without combination with azithromycin in COVID-19 also showed the beneficial and positive results.²⁷ In contrast, some studies showed no evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection.²⁸ On the other hand, both drugs cause QT prolongation to some extent, and combining two potential QT-prolonging drugs is thought to result in serious implications like fatal cardiac arrhythmias especially in people with preexisting cardiac illness. Together ACC, AHA and Heart rhythm society (HRS) on 8th April 2020 jointly came with the new guideline "Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 19) Treatment," recommending for careful consideration of those drugs in patients with preexisting cardiovascular disease.²⁹

In view of high mortality of severe disease particularly due to complications like disseminated intravascular coagulation, venous thromboembolism, and pulmonary embolism some experts believe that using anticoagulants like heparin in selected patients of COVID-19 decreases the mortality. One such study done at Hubei, China reported that use of heparin for patients with D-dimer > 6 fold of upper limit of normal and sepsis-induced coagulopathy (SIC) score ≥ 4 results in a significant decrease in 28 days mortality compared to nonusers.³⁰

More importantly, the COVID-19 pandemic and the lockdown in various parts of the globe might have direct and indirect detrimental consequences in cardiovascular care. The number of elective diagnostic and therapeutic catheterization procedures has decreased significantly throughout the world. Also, lack of transportation to a health care facility, fear of hospital visit, unavailability of cardiology outpatient clinics and cessation of regular cardiovascular medications might forecast a significant surge of load in cardiology services in the post locked down era. These issues can be sorted by adopting virtual consultation and treatment measures like telemedicine and video conferencing. Mass awareness regarding the danger signs and symptoms of serious cardiovascular diseases, development of proper patient transfer and referral systems in the current crisis will also help to reduce the anticipated burden on cardiovascular care in the post locked down era.

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