Original Research Paper

Volume - 11 | Issue - 01 | January - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medical Science

COVID AND CARDIOVASCULAR MANAGEMENT- KEY CHALLENGES AND THERAPEUTIC CONSIDERATIONS

Dr. Paras Jain Director Jain Hospital, Hanumangarh.

KEYWORDS :

The pandemic caused by a novel coronavirus (COVID-19) has disrupted complete global order affecting millions socially, economically, psychologically, and medically. Patients with pre-existing cardiovascular disease and risk factors are more likely to experience adverse outcomes associated with the novel coronavirus disease-2019 (COVID-19) [1]. Even though 80% of all COVID-19 patients have only mild or moderate symptoms, the case-fatality ratio is extremely variable. This variability may be accounted for the testing practices, case definition, access to the health system, and other unknown factors[2]. Patients with the co-existing condition of cardiovascular disease, obesity, diabetes, and old age are at higher risk of infection, morbidity, and mortality due to COVID-19. Such patients are at 2-3-fold higher risk of getting infected with COVID-19. Poor functioning of the immune system due to elevated levels of blood glucose seems to be one of the primary causes of the increased risk of COVID-19 infection in diabetes patients[3]. The concurrent occurrence of diabetes with cardiovascular disease and old age has further complicated the scenario. Additionally, there has been an increase in reports of acute and de novo cardiac presentations such as myocarditis, arrhythmia, and heart failure in patients without prior cardiovascular disease or significant risk factors. This may be possibly due to an accentuated host immune response and cytokine storm[1]. The interaction between COVID-19 and the cardiovascular system has been a subject of distinct attention.

THE VIRUS

Essentially, coronaviruses, are from a large family of single-stranded enveloped RNA viruses, that share 79.6% genomic sequence identity with severe acute respiratory syndrome coronavirus (SARS- CoV) and 96.0% similarity with the bat coronavirus RaTG13. Coronaviruses possess a crown-like morphology, that involves four structural proteins known as spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. N protein is a positive-sense, single-stranded RNA that surrounds the viral genome. This single-stranded RNA functions as both a genome and an mRNA. These coronaviruses can be categorized into four genera: α, β, γ, and δ. Amongst them, α and β- coronaviruses are pathogenic to humans [4]. The viral entry is via S protein. The binding of the viral S protein to angiotensin-converting enzyme 2 (ACE2) triggers the entry of the virus into the host cell. ACE2 is part of the renin-angiotensin-aldosterone system (RAAS) which cleaves angiotensin-II – a vasoconstrictor into angiotensin – a vasodilator. Therefore, the interaction between the S protein and ACE2 seems to be a promising therapeutic target for the development of vaccines, neutralizing antibodies, and antiviral compounds[4].

CARDIOVASCULAR CHALLENGES ASSOCIATED WITH COVID-19

ACE2 is highly expressed in the lung (principally type II alveolar cells7) and appears to be the predominant port of entry. Additionally, ACE2 is also highly expressed in the heart, counteracting the effects of angiotensin II in states with excessive activation of the renin-angiotensin system, such as hypertension, congestive heart failure, and atherosclerosis. In addition to the heart and lung, ACE2 is expressed in the intestinal epithelium, vascular endothelium, and kidneys, thus providing a possible link for the mechanism for the multiorgan dysfunction that can be seen with SARS-CoV-2 infection[5]. There is increasing evidence linking COVID-19 with increased COVID-19 is predominantly a lung disease, where initial local damage is followed by an intense cytokine storm that stems from an imbalance of T cells activation with dysregulated release of interleukin (IL)-6, IL-17, and other cytokines[6]. Alternatively, and as per some reports, COVID-19 can also initiate with signs of severe coronary artery disease or myocarditis in the absence of a history of cardiovascular diseases, or the presence of isolated cardiovascular risk factors[5,7]. Immune dysregulation occurring due to viral infection results in precipitation of the controlled cardiovascular condition into an uncontrolled cardiac condition. A possible incompatibility of the antiviral drugs with statins, the risk induction of cardiotoxicity by anti-inflammatory agents such as hydroxychloroquine and chloroquine, and water retention and ionic imbalance due to corticosteroids, such as methylprednisolone, further complicates the therapy for the cardiac situation in COVID patients. Another major issue pertaining to the cardiovascular condition in COVID patients is the inappropriate activation of the coagulation cascade resulting in elevated levels of d-dimers and fibrinogen. The use of heparin has potentially improved the prognosis, especially in COVID-19 patients with circulating D-dimer >3.0 mg/mL. It is postulated that sustained inflammatory response associated with vascular inflammation results in the activation of the coagulation and endothelial dysfunction. A critical manifestation of this activation of thrombosis is that in the COVID-19 patients, the site of thrombosis is in the lungs rather than in the lower limbs. This is even true for patients without any specific risk factors and/or history of thromboembolism. Thus, coagulation parameters need to be carefully monitored in COVID-19 patients, especially in patients with severe disease[7]. Low molecular weight heparin is recommended for COVID-19 patients with elevated d-dimer levels[8]. Thus, in view of these complications in COVID-19, cardiologists face a critical challenge for the clinical management of cardiovascular diseases, and establishing a guideline for cardiovascular manifestations in COVID-19 becomes pertinent.

Management Of Various Cardiovascular Manifestations In COVID-19

- **Hypertension Management**

ACE inhibitors are important therapeutic agents used in the management of hypertension. Theoretically, ACE inhibitors result in the upregulation of ACE2 activity in COVID-19 patients resulting in a higher functional substrate for the virus to bind to and cause severe organ damage. However, this has not been verified from the clinical studies. Studies on the COVID-19 patients have shown that usage of ACE inhibitors has not been associated with the probability of SARS-CoV-2 infection[9]. Thus, it is recommended that treatment with ACE inhibitors should be continued in patients for hypertension management. Cardiac societies like ACC and ESC, also recommend the non-withdrawal of ACE inhibitors from the therapeutic arsenal of hypertension[2].

- **Acute Coronary Syndrome (ACS)**

There is a possibility of under-diagnosis of ACS in COVID-19 patients due to elevated levels of troponin (7-28%), even in absence of ischemic etiology. Thus, it is recommended that serial troponin measurements are carried out in order to determine whether the myocardial injury shown by the elevated troponin value is acute or chronic. ECG and clinical history should also be taken into consideration for establishing the nature of the myocardial injury. As a general rule without any COVID test, each patient must be considered as a COVID-19 patient with special precautions in place for handling patients with fever. There is also increased chances of coronary plaque rupture in patients with coronary artery diseases secondary to virally induced systemic inflammation. Plaque stabilizing agents (aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors) is recommended as a possible therapeutic strategy. In confirmed COVID-19 positive low-risk STEMI patients, thrombolysis is the recommended treatment of choice. Catheterization should be carried only as a rescue strategy. While, for carrying out catheterization in high-risk COVID positive patients, the availability of protective kits for all the involved medical staff is mandatory. In the case of NSTEMI patients, conservative management should be followed with due

consideration given to the possible thrombocytopenia in COVID-19 patients for establishing a revascularisation therapy[10].

- **Myocardial Injury (MI)**

Diagnosis of MI is also associated with the determination of troponin levels, which are also high in the case of COVID-19. Thus, leading to a poor prognosis. Autopsy studies of the COVID-19 patient have led to the establishment of the fact that viral particles are not present in the myocardium even though there are a large number of ACE-2 receptors in the myocardium and cardiac epithelium. Macrophages from the lungs carry the viral particles to the myocardium. Largely, cytokine storms induced by the SARS- CoV, lead to increased vascular permeability and myocardial edema with transient damage to the myocardium. It is essential to carry out ECG, chest radiography for the diagnosis of MI in COVID-19 patients. Sinus tachycardia is commonly seen in COVID-19 patients; however, it may even be present in the absence of myocardial injury. Non-localizing ST changes (typically concave in shape) and/or non-specific T-wave changes are indicative of underlying myocardial involvement. New conduction abnormalities, such as atrioventricular block, sinus arrest, and QRS prolongation, and arrhythmias (atrial or ventricular) are suggestive of underlying cardiac involvement. Chest radiography along with the clinical symptoms may be used to distinguish pulmonary edema from viral pneumonia. Ventricular dysfunction (systolic or diastolic) with or without dilatation of the ventricles indicates a significant myocardial disruption. Regional wall motion abnormalities may be seen and are indicative of myocarditis when observed at rest and seen in combination with non-localizing ST changes on ECG and a positive troponin. Viral myocarditis frequently affects the basal inferolateral wall. Additionally, features like, increased ventricular wall thickness, pericardial effusion, and intracardiac thrombus formation may also be seen. For the management of MI, current guidelines for the treatment of viral myocarditis should be used, including the use of standard heart failure therapies which include diuretics, ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists along with supportive measures. Prednisolone has shown some benefit in a few isolated cases, however routine usage of the steroid may cause long-term side effects in the patients, hence, it is not encouraged to use them[11].

- **Thrombosis And Anticoagulation**

COVID-19 has been found to increase the D-dimer levels, fibrin degradation products, and prothrombin time (PT) prolongation that predispose the patient to thrombotic events. Although, it is still unclear whether these changes are a consequence of SARS-CoV-2 or a result of systemic inflammatory response syndrome (SIRS). Thus, patients with COVID-19 are at increased risk of venous thrombotic events and the use of prophylactic anticoagulation is recommended. Low molecular weight heparin is recommended to be administered[12]. It is suggested that patients with structural and functional abnormalities should have a repeated echocardiogram in 1-3 months after discharge and should have follow up for a minimum of six months. In cases where left ventricular (LV) recovery is delayed beyond three months, heart failure therapy should be continued for a minimum of six months to a year. Long-term therapy heart failure therapy is recommended for patients with persistent LV dysfunction, conduction abnormalities, or those with evidence of myocardial scar[2].

- **Heart failure (HF) and COVID-19**

The mortality rate is as high as 10.5% in COVID patients with pre-existing cardiovascular conditions as compared to the fatality rate of 2.3% in the general population. Respiratory infection is a common trigger of HF decompensation[13]. Patients with chronic cardiovascular conditions are predisposed to respiratory infection ad further complications. Regular follow up via telemedicine is recommended in patients with stable chronic cardiac disorders. Elective procedures in such cases should also be deferred in order to minimize the exposure to the viral infection. A routine flu vaccine is also recommended for such patients.

Protection to healthcare staff and other patients should be ensured during clinical evaluation of the patients with unstable patients. Echocardiography should be used with adequate precautions for person and equipment to maintain barrier based on resources available. Continuation of HF guideline-directed medical therapies is generally recommended despite controversies regarding the effect of ACE inhibitors and angiotensin receptor blockers on COVID-19. Withdrawal of renin-angiotensin system inhibitors should only be based on the clinical requirement of the case. A multi-disciplinary team that includes an infectious disease consultant and intensive care specialist and pulmonologist should be engaged in HF COVID-19 positive cases. Therapeutic management based on the clinical condition can be opted. Hydroxychloroquine has been proposed to treat COVID-19 based on *in-vitro* data and a small open-label study with significant methodological limitations, however further studies are essential for widespread usage. As mentioned earlier, it is important to keep in mind that hydroxychloroquine could prolong the QT interval and cause arrhythmias. Antiviral therapies especially hold promise however further studies are required. In selected cases, immunosuppression has been used as salvage therapy, however, given concerns that steroids may prolong viral persistence, steroid treatment is not routinely recommended in all cases. Anti-inflammatory agents e.g. interleukin-6 inhibitors are under investigation in patients with severe COVID-19. Convalescent plasma from recovered COVID-19 patients has been approved by the FDA and warrants further study. Mechanical circulatory support may be indicated in selected patients with refractory shock[14].

CONCLUSION

COVID-19 pandemic has completely changed the global order, economically as well as medically. Essentially, COVID-19 is a lung disease however, a cytokine storm or hyperimmune reaction leads to various systemic impacts on different organs of the body especially affecting the cardiac. The patients with the pre-existing cardiac disorder are at higher risk of getting infected and acquiring the severe form of disease and complications, often requiring treatment in the intensive care unit. There is an elevated risk of precipitation of thrombotic manifestation, local or systemic, along with prolongation of QT interval. Further, lack of clinical evidence on the possible increased side effects of ACE inhibitors and sartans has led to a general consensus that their usage should not be discontinued in case of COVID-19 positive patients with cardiac complications.

Given the lack of a vaccine or proven treatment for COVID-19 and stress on the medical facility, it is essential to follow standard guidelines for the treatment. However, due consideration must be taken based on the clinical symptoms of the patient as well. There is an urgent need for effective treatment and preventative strategies, a concerted effort must be made by researchers globally to investigate and integrate biological and clinical findings related to COVID-19.

REFERENCES

1. Ganatra S, Dani SS, Shah S, et al. Management of Cardiovascular Disease During Coronavirus Disease (COVID-19) Pandemic. *Trends in Cardiovascular Medicine*. 2020;30(January):315–325.
2. Prabhakaran D, Perel P, Roy A, et al. Erratum: Correction: Management of Cardiovascular Disease Patients With Confirmed or Suspected COVID-19 in Limited Resource Settings (Global heart (2020) 15 1 (44)). *Global heart*. 2020;15(1):54. doi:10.5334/gh.885
3. Bhaskar S, Rastogi A, Chattu VK, et al. Key Strategies for Clinical Management and Improvement of Healthcare Services for Cardiovascular Disease and Diabetes Patients in the Coronavirus (COVID-19) Settings: Recommendations From the REPROGRAM Consortium. *Frontiers in Cardiovascular Medicine*. 2020;7(June):1-10. doi:10.3389/fcvm.2020.00112
4. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nature Reviews Cardiology*. 2020;17(9):543-558. doi:10.1038/s41569-020-0413-9
5. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and Cardiovascular Disease. *Circulation*. 2020;2019:1648-1655. doi:10.1161/CIRCULATIONAHA.120.046941
6. Mai F, del Pinto R, Ferri C. COVID-19 and cardiovascular diseases. *Journal of Cardiology*. 2020;76(5):453-458. doi:10.1016/j.jjcc.2020.07.013
7. Fried JA, Ramasubbu K, Bhatt R, et al. The Variety of Cardiovascular Presentations of COVID-19. *Circulation*. 2020;141(23):1930-1936. doi:10.1161/ CIRCULATIONAHA.120.047164
8. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of heparin and its derivatives: A systematic review. *Advances in Pharmacological Sciences*. 2015;2015. doi:10.1155/2015/507151
9. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. *New England Journal of Medicine*. 2020;382(25):2441-2448. doi:10.1056/nejmoa2008975
10. Lippi G, Plebani M, Michael B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta*. 2020;506(January):145-148.
11. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *European Heart Journal*. 2013;34(33):2636-2648.doi:10.1093/eurheartj/eht210
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis*.2020;18(5):1094-1099. doi:10.1111/jth.148 17
13. Wu Z MJM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242.
14. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. *Circulation*. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509