Review Article

COVID-19 and the Cardiovascular System

Author: Bernard Gersh

Bernard Gersh, M.B., Ch.B., D.Phil. Professor of Medicine, Mayo Clinic, Rochester, Minnesota. Gersh.Bernard@mayo.edu

Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less".
(Quotation from Marie Curie 1867-1934).

Introduction

After the first case of COVID-19 (SARS-COV-2) was first reported in 2019 in Wuhan China(1) it has developed into a global pandemic with an enormous impact upon mortality, morbidity, medical research, socioeconomic status, and with implications for virtually all aspects of society(2,3). As the pandemic evolves we have had to accept the limitations of our current knowledge regarding its epidemiology, methods of transition, the vulnerability of certain patient groups, and the variability in clinical responses to infection in addition to the challenges of identifying new therapies and vaccines. One fact is indisputable – progress has been rapid but there is nonetheless so much that we still do not know.

In comparison to other coronavirus infections, it has become unequivocally evident that COVID-19 infection can vary from an asymptomatic carrier state to a fulminant systemic infection affecting multiple organ systems including the cardiovascular system, in addition to the most common manifestation, namely lung involvement(4-7). In a recent multinational evaluation of echocardiography in 1216 COVID patients, 55% had an abnormal echocardiogram(8).

SARS-coronavirus-2 is caused by binding of the viral receptor --- protein to the human angiotensin-converting enzyme 2 (ACE-2) receptor in the lung (type 2 activation cells), and this is the predominant portal of entry(6). ACE-2 is, however, highly expressed in the heart in addition to the vascular and coronary endothelium, the kidneys, and intestinal endothelium – an explanation for the protean manifestations of this disease(4,9). The clinical picture is driven in part by the extent of viral load and organ infiltration and by the inflammatory and at times hyperinflammatory cytokine response of the host. (Figure)

In patients with cardiac injury/involvement, the pathophysiology is multifactorial due to "direct myocardial injury", the effects of respiratory failure and hypoxemia, and the consequences of a hyperinflammatory response with cytokine storm. Besides, the involvement of the coronary endothelium and vasculature in concert with coagulopathy may dominate the clinical picture and natural history in some patients(4,8-10). (Figure)

COVID-19 in Patients with Pre-existing Cardiovascular Disease

As is the case in patients with SARS and MERS, cardiovascular comorbidities are common in older infected patients(6,11). In a meta-analysis of 6 studies, prevalence

rates of hypertension, diabetes, known cardiovascular or cerebrovascular disease ranged from 9.7 to 17.1%(4,6,12). In patients with severe or critical diseases admitted to ICUs, there appears to be a strong association between obesity, prior hypertension, diabetes mellitus, coronary artery disease, and worse outcomes perhaps mediated by vascular aging, diminished renal function, and reduced cardiovascular reserves(6,13,14). Functional impairment of the immune system is secondary to aging and other comorbidities including obesity may be a contributing factor that may modify the response of the host to infection.

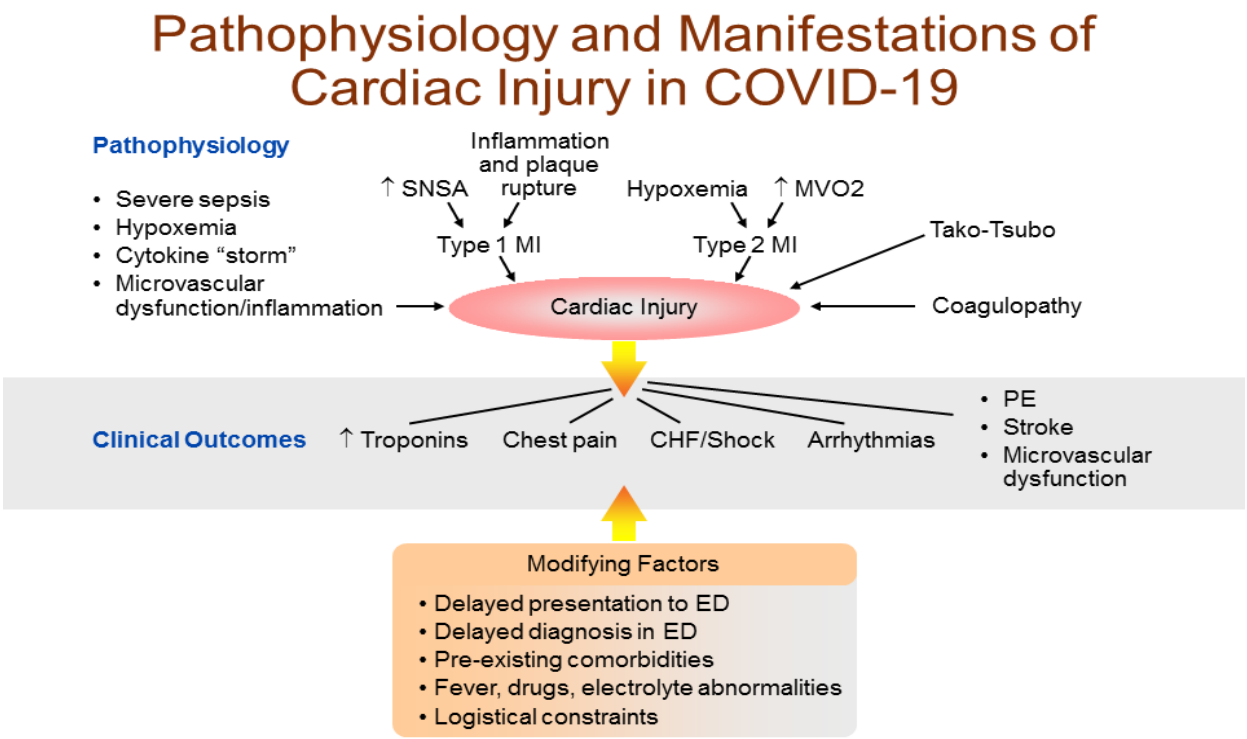
COVID-19 and Myocardial Injury

Multiple studies have demonstrated that myocardial injury as demonstrated by increased levels of hs-troponin is common (17% of patients in one study but 46% of patients had died and only 1% among survivors)(13). It has been postulated that myocardial injury in the majority may be associated with other inflammatory biomarkers reflecting cytokine storm, multiorgan dysfunction, and sepsis, and, as such, it is a nonspecific marker of overall disease severity. (Figure).

It is possible that in another smaller population of patients, particularly among those with preceding cardiac symptoms, a myocardial injury may be the consequence of viral myocarditis and microvascular obstruction due to inflammation and thrombosis(4-6,10). Other causes of myocardial injury include acute myocardial infarction (Type 1 due to plaque rupture or Type 2 myocardial infarction) secondary to an imbalance between oxygen demand and supply, exacerbated by hypoxemia, and the Takotsubo syndrome(6). A recent study from the USA demonstrated a significant increase in Takotsubo syndrome in patients presenting with acute coronary syndromes compared to a similar period before the pandemic suggesting that psychological, social, and economic stress related to the COVID-19 pandemic may be a precipitant(15).

COVID-19 and Coagulopathy

Multiple studies have demonstrated abnormal coagulation parameters causing a generalized coagulopathy. This is a powerful predictor of mortality and has also been associated with stroke, pulmonary



emboli, increasing respiratory failure, and extensive cardiac injury(4,6).

COVID-19 and Heart Failure

Although in a minority, there are numerous reports(10,16) in which the clinical picture has been dominated by cardiogenic shock and pump failure and the differentiation from ARDS is difficult and frequently requires right heart catheterization. The etiology is multifactorial; underlying inflammatory state, hypoxia, and hemodynamic impairment or possibly a direct COVID-19 infiltration but this remains unknown(11). Irrespective, the presence of heart failure is significant and not surprisingly a major predictor of an adverse outcome.

Arrhythmias

Atrial and ventricular arrhythmias are well described in patients with COVID-19 and here again, the explanations are likely multifactorial(17). An additional factor is drug-interactions, e.g., hydroxychloroquine and azithromycin, in patients with severe sepsis, electrolyte and metabolic abnormalities, and other factors prolonging the QT interval(4,6,10,18). Atrial fibrillation is a well-documented adverse prognostic factor.

Impact on Management of non-COVID Cardiovascular Disease

It should be emphasized that even during the height of the pandemic; the majority of patients requiring care for ischemic heart disease may not be infected with COVID-19. Management of acute coronary syndromes during the pandemic, however, is challenging from several different perspectives. The first is the differentiation of the cardiovascular features of COVID-19 from those of an acute coronary syndrome due to plaque rupture and erosion, or a Type 2 infarction due to demand-supply imbalance(16,19). Secondary, pressures on staff and facilities in emergency medical systems may result in both patient and system delays in making a diagnosis. Many reports from around the world have drawn attention to the striking reduction in STEMI admissions, probably related in part to a reluctance to seek medical attention in addition to misdiagnoses in the ED(16,20).

A separate issue is a balance between the optimal and invasive approaches to the management of STEMI, irrespective of whether patients are infected with COVID or not, and the risk to healthcare workers and contamination of laboratory facilities. A fibrinolytic-based strategy including the pharmacoinvasive approach is likely to be widely used in certain regions and situations(16,19) but it has its limitations. Although primary PCI remains the preferred approach to reperfusion therapy, this at times may not be feasible or the most effective approach during the pandemic(21).

In patients with a stable coronary disease requiring revascularization, there is a considerable discussion regarding performing a PCI-based approach even if this is suboptimal anatomically, given the logistical constraints of performing coronary bypass surgery in the pandemic milieu.

Cardiac Transplantation

COVID-19 has generated new challenges for the management of transplant recipients who are immunocompromised(6,22,23). However, there is a dearth of information regarding outcomes in this highly vulnerable patient population. Other issues include the management of patients on the waiting list and the balance between the risks of new recipients developing COVID-19 versus the risk of postponing transplantation at the cost of increased mortality due to transplantation of sicker patients at a later date.

Cardiometabolic Consequences of Social Isolation and Emotional Stress

Prevention and large scale containment of COVID-19 is a key strategy for reducing the potential health consequences of this pandemic(24). Nonetheless, these stringent measures come at a price, and the negative association between physical isolation, depression, and cardiovascular disease, especially in older individuals living alone, should not be underestimated. The guidelines for prevention should be modified to incorporate settings of social isolation and poor social support in patients with and without known cardiovascular disease. These situations coupled with the effects of emotional stress increase cardiovascular risk by blood pressure elevation, reduced level of aerobic exercise, weight gain, increased cigarette smoking, and an inability in some populations to get prescriptions filled. As is the case in other risk factor management strategies, the burden is greater in patients of lower socioeconomic status. There is a potentially important role in the use of digital technologies and telehealth in individuals lacking social support.

Prevention and Treatment

Regarding the involvement of the cardiovascular system in COVID-19, prevention, and treatment fall under the umbrella of multiple approaches, including 150 vaccine strategies, currently under evaluation around the world(25). As such, this will not be addressed in any detail for this review which is focused on cardiovascular disease.

Management of patients with documented cardiovascular involvement is primarily supportive including ventilation and control of hypoxemia, pulmonary artery catheterization in patients with hemodynamic compromise, the use of ECMO in selected patients, anti failure therapy, and electrocardiographic monitoring for evidence of drug-induced cardiotoxicity(6,17). There appears to be a strong rationale for anticoagulant therapy although there is no consensus as to which drugs and the optimal doses. The controversy surrounding the contribution of angiotensin-converting inhibitors and angiotensin receptive blocker therapy in patients previously treated with these agents has largely been resolved(6,26). Clinical trials strongly suggest that these agents should not be discontinued in patients in whom these drugs have been prescribed for valid reasons. Hydroxychloroquine has not withstood the rigorous scrutiny of clinical trials in hospitalized patients with severe disease and also in those with mild disease(7,27) and probably has no role in the therapy of COVID 19, despite widespread media attention.

Conclusions

The pandemic continues to evolve and there is now widespread recognition of the effects of COVID-19 on multiple organ systems. We have also learned that the cardiovascular impact of COVID-19 is far greater than what would be expected based on data showing only limited viral load in myocardial tissue(4). A growing concern that will require intensive further investigation will be the presence of chronic disease e.g. interstitial fibrosis and the specter of late heart failure in COVID-19 survivors. A recent CMR study from Germany demonstrated cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independent of pre-existing conditions, and the severity and overall course of the initial illness(28). The long-term impact of viral load without evidence of inflammatory myocarditis possibly leading to non-ischemic cardiomyopathy is unknown and will be a focus of further study(29). What should also

be emphasized is the impact of the pandemic on the management of cardiovascular disease in non-COVID infected patients and the social and cardiometabolic implications of social isolation and containment measures. Sadly, the pandemic has widened pre-existing socioeconomic disparities in cardiovascular health and imposes an additional strain on structures and systems that are already struggling to deal with these socioeconomic disparities. The challenges and the solutions will vary among countries and regions and, as such, "one size will not fit all".

References

1. Lu H, Stratton CW, Tang Y-W. An outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92:401-402.
2. Byrd James B, Bello N, Meyer Michelle N. Pandemic Pandemonium. Circulation 2020;141:2045-2047.
3. Narula N, Singh Harsimran S. New York City Innocence Lost. Circulation 2020;141:2039-2041.
4. Akhmerov A, Marbán E. COVID-19, and the Heart. Circulation Research 2020;126:1443-1455.
5. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. JAMA Cardiology 2020;5:751-753.
6. Clerkin Kevin J, Fried Justin A, Raikhelkar J et al. COVID-19, and Cardiovascular Disease. Circulation 2020;141:1648-1655.
7. Gupta A, Madhavan MV, Sehgal K et al. Extrapulmonary manifestations of COVID-19. Nature Medicine 2020;26:1017-1032.
8. Dweck MR, Bularga A, Hahn RT et al. Global evaluation of echocardiography in patients with COVID-19. European Heart Journal - Cardiovascular Imaging 2020.
9. Gupta Ajay K, Jneid H, Addison D et al. Current Perspectives on Coronavirus Disease 2019 and Cardiovascular Disease: A White Paper by the JAHA Editors. Journal of the American Heart Association 2020;9:e017013.
10. Oren O, Kopecky S, TJ G, Gersh BJ, Blumenthal Roger S. Coronavirus disease 2019 (COVID-19): epidemiology, clinical spectrum, and implications for the cardiovascular clinician. ACC.org Expert Analysis, 2020.
11. Fried Justin A, Ramasubbu K, Bhatt R et al. The Variety of Cardiovascular Presentations of COVID-19. Circulation 2020;141:1930-1936.
12. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine 2020;46:586-590.
13. Organization WH. Report of the Who-China Mission on coronavirus disease 2019 (COVID-19). 2020.
14. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
15. Jabri A, Kalra A, Kumar A et al. Incidence of Stress Cardiomyopathy During the Coronavirus Disease 2019 Pandemic. JAMA Network Open 2020;3:e2014780-e2014780.

16. Welt FGP, Shah PB, Aronow HD et al. Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic. Journal of the American College of Cardiology 2020;75:2372.
17. Oren O, Yang Eric H, Gluckman Ty J, Michos Erin D, Blumenthal Roger S, Gersh Bernard J. Use of Chloroquine and Hydroxychloroquine in COVID-19 and Cardiovascular Implications. Circulation: Arrhythmia and Electrophysiology 2020;13:e008688.
18. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clin Proc 2020;95:1213-1221.
19. Mahmud E, Dauerman HL, Welt FGP et al. Management of Acute Myocardial Infarction During the COVID-19 Pandemic. Journal of the American College of Cardiology 2020:27295.
20. Driggin E, Madhavan MV, Bikdeli B et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. Journal of the American College of Cardiology 2020;75:2352.
21. Daniels Matthew J, Cohen Mauricio G, Bavry Anthony A, Kumbhani Dharam J. Reperfusion of ST-Segment–Elevation Myocardial Infarction in the COVID-19 Era. Circulation 2020;141:1948-1950.
22. DeFilippis Ersilia M, Farr Maryjane A, Givertz Michael M. Challenges in Heart Transplantation in the Era of COVID-19. Circulation 2020;141:2048-2051.
23. Latif F, Farr MA, Clerkin KJ et al. Characteristics and Outcomes of Recipients of Heart Transplant With Coronavirus Disease 2019. JAMA Cardiol 2020.
24. Oren O, Gersh BJ, Blumenthal RS. Anticipating and curtailing the cardiometabolic toxicity of social isolation and emotional stress in the time of COVID-19. Am Heart J 2020;226:1-3.
25. Bikdeli B, Madhavan MV, Gupta A et al. Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research. Thromb Haemost 2020;120:1004-1024.
26. Messerli Franz H, Siontis George CM, Rexhaj E. COVID-19 and Renin Angiotensin Blockers. Circulation 2020;141:2042-2044.
27. Skipper CP, Pastick KA, Engen NW et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med 2020:M20-4207.
28. Puntmann VO, Carerj ML, Wieters I et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology 2020.
29. Lindner D, Fitzek A, Bräuninger H et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiology 2020.