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Original Article

Cardiovascular disease and COVID-19

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A B S T R A C T

Background and aims: Many patients with coronavirus disease 2019 (COVID-19) have underlying cardiovascular (CV) disease or develop acute cardiac injury during the course of the illness. Adequate understanding of the interplay between COVID-19 and CV disease is required for optimum management of these patients.

Methods: A literature search was done using PubMed and Google search engines to prepare a narrative review on this topic.

Results: Respiratory illness is the dominant clinical manifestation of COVID-19; CV involvement occurs much less commonly. Acute cardiac injury, defined as significant elevation of cardiac troponins, is the most commonly reported cardiac abnormality in COVID-19. It occurs in approximately 8–12% of all patients. Direct myocardial injury due to viral involvement of cardiomyocytes and the effect of systemic inflammation appear to be the most common mechanisms responsible for cardiac injury. The information about other CV manifestations in COVID-19 is very limited at present. Nonetheless, it has been consistently shown that the presence of pre-existing CV disease and/or development of acute cardiac injury are associated with significantly worse outcome in these patients.

Conclusions: Most of the current reports on COVID-19 have only briefly described CV manifestations in these patients. Given the enormous burden posed by this illness and the significant adverse prognostic impact of cardiac involvement, further research is required to understand the incidence, mechanisms, clinical presentation and outcomes of various CV manifestations in COVID-19 patients.

1. Introduction

The emergence of novel coronavirus, officially known as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), has presented an unprecedented challenge for the healthcare community across the world. High infectivity, ability to get transmitted even during asymptomatic phase and relatively low virulence have resulted in rapid transmission of this virus beyond geographic regions, leading to a pandemic. The first case of this disease, known as coronavirus disease 2019 (COVID-2019), occurred on December 8, 2019 in the Hubei province of China [1]. Since then, within a short span of just over 3 months, the infection has spread to 177 countries/area/territories across the world, with 266073 confirmed cases and 11184 deaths (World Health Organization statistics as on March 21, 2020) [2] .

Respiratory involvement, presenting as mild flulike illness to potentially lethal acute respiratory distress syndrome or fulminant pneumonia, is the dominant clinical manifestation of COVID-19. However, much like any other respiratory tract infection, pre-existing cardiovascular disease (CVD) and CV risk factors enhance vulnerability to COVID-19. Further, COVID-19 can worsen underlying CVD and even precipitate *de novo* cardiac complications.

This review is aimed at providing overview of various CV manifestations in patients presenting with COVID-19. The impact of pre-existing CVD and new onset cardiac complications on clinical outcomes in these patients is also discussed. Since our understanding on this subject is only evolving at this stage, the information contained in the subsequent text is based mainly on the limited early experience with COVID-19 and learnings from the previous coronavirus illnesses, namely SARS and Middle-East Respiratory Syndrome (MERS).

2. Search methods

A literature search was done using PubMed and Google search engines for original and review articles, advisories from professional societies, and expert commentaries published since the

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Table 1
Cardiovascular complications in coronavirus disease 2019.

Manifestation	Incidence	Remarks
Acute cardiac injury* (most commonly defined as elevation of cardiac troponin I above 99th percentile upper reference limit)	8–12% on average [10]	• Most commonly reported cardiovascular abnormality • Can result from any of the following mechanisms- •Direct myocardial injury •Systemic inflammation •Myocardial oxygen demand supply mismatch •Acute coronary event •Iatrogenic • Strong adverse prognostic value
Acute coronary event	Not reported, but appears to be low	Potential mechanisms- • Plaque rupture due to inflammation/increased shear stress • Aggravation of pre-existing coronary artery disease
Left ventricular systolic dysfunction	Not reported	Any of the causes of myocardial dysfunction mentioned above can lead to acute left ventricular systolic dysfunction
Heart failure	Reported in one study- 52% in those who died, 12% in those who recovered and were discharged [5]	• Any of the causes of myocardial dysfunction mentioned above can lead to acute heart failure • Increased metabolic demand of a systemic disease can cause acute decompensation of pre-existing stable heart failure
Arrhythmia	16.7% overall; 44.4 in severe illness, 8.9% in mild cases [8]	Both tachyarrhythmia and bradyarrhythmia can occur but exact nature not described
Potential long-term consequences	Too early to assess	Too early to ascertain for coronavirus disease 2019. However, patients recovering from a similar earlier illness- Severe Acute Respiratory Syndrome- continued to have long-term abnormalities of lipid and glucose metabolism and of cardiovascular homeostasis [12]

* Acute cardiac injury is a non-specific term with significant overlap with other cardiovascular manifestations; however, it is listed here because of how reporting has been done in most of the studies on coronavirus disease 2019.

onset of the current COVID-19 epidemic. Search terms “COVID-19” and “coronavirus” were used in combination with “cardiac”, “cardiovascular”, “arrhythmia”, “myocardial infarction”, “troponin” and “heart failure”. Relevant cross-references for previous studies about SARS and MERS were also reviewed.

2.1. Pathogenic considerations

SARS-CoV-2 is caused by a novel enveloped RNA beta-coronavirus. Seven species of these beta-coronaviruses are known to cause human infections, with four mainly causing mild flulike symptoms and the remaining three resulting in potentially fatal illnesses (SARS, MERS and the ongoing COVID-19). Although respiratory tract is the primary target for SARS-CoV-2, CV system may get involved in several different ways. Following are the common mechanisms responsible for CV complications in COVID-19 [3,4]-

1. *Direct myocardial injury*- SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 (ACE2), a membrane bound aminopeptidase which is highly expressed in heart and lungs. ACE2 plays an important role in neurohumoral regulation of CV system in normal health as well as in various disease conditions. The binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signaling pathways, leading to acute myocardial and lung injury [3,4].
2. *Systemic inflammation*- More severe forms of COVID-19 are characterized by acute systemic inflammatory response and cytokine storm, which can result in injury to multiple organs leading to multiorgan failure. Studies have shown high circulatory levels of proinflammatory cytokines in patients with severe/critical COVID-19 [5,6].
3. *Altered myocardial demand*-supply ratio- Increased cardiometabolic demand associated with the systemic infection coupled with hypoxia caused by acute respiratory illness can impair myocardial oxygen demand-supply relationship and lead to acute myocardial injury.
4. *Plaque rupture and coronary thrombosis*- Systemic inflammation as well as increased shear stress due to increased coronary blood flow can precipitate plaque rupture resulting in acute myocardial infarction. Prothrombotic milieu created by systemic inflammation further increases the risk.
5. *Adverse effects of various therapies*- Various antiviral drugs, corticosteroids and other therapies aimed at treating COVID-19 can also have deleterious effects on the CV system.
6. *Electrolyte imbalances*- Electrolyte imbalances can occur in any critical systemic illness and precipitate arrhythmias, esp. in patients with underlying cardiac disorder. There is particular concern about hypokalemia in COVID-19, due to interaction of SARS-CoV-2 with renin-angiotensin-aldosterone system [7]. Hypokalemia increases vulnerability to various tachyarrhythmias.

2.1.1. Role of underling CV comorbidities

The patients with pre-existing CVD appear to have heightened vulnerability to develop COVID-19 and tend to have more severe disease with worse clinical outcomes [1,4,6,8]. Various CV risk factors also adversely affect porgnosis of these patients, although they do not seem to increase likleihood of developing the infection. A meta-analysis of six published studies from China including 1527 patients with COVID-19 reported 9.7%, 16.4% and 17.1% prevalence of diabetes, cardio-cerebrovascular disease and hypertension respectively [4]. Although the prevalence of diabetes and hypertension in this cohort was same as in the Chinese general population, the prevalence of cardio-cerebrovascular disease was considerably higher. More importantly, the presence of diabetes, cardio-cerebrovascular disease and hypertension was associated with a 2-fold, 3-fold and 2-fold greater risk of severe disease or requiring intensive care unit (ICU) admission, suggesting prognostic impact of these comorbidities. A much larger report from the Chinese Center for Disease Control and Prevention described clinical outcomes in 44672 confirmed cases of COVID-19 [1]. The overall case fatality rate (CFR) was 2.3% in the entire cohort but significantly higher (6%, 7.3% and 10.5% respectively) in patients with hypertension, diabetes and CVD.

Although data is lacking, the prevalence of various CV

comorbidities and their impact on clinical outcomes seem to vary considerably across different geographic locations. The CFRs have been lower in China outside Hubei province and many other countries but much higher in some European nations [2]. A small report including 21 patients from Washington, United States of America presented a particularly grim scenario [9]. Comorbidities were common in this cohort, with diabetes present in 33.3% and congestive heart failure in 42.9%. Acute cardiac dysfunction occurred in 33.3% patients and 52.4% patients died. However, the overall CFR in the United States seems to be much lower (201 deaths out of 15219 confirmed cases) [2], although it is likely to rise as many of the patients are currently hospitalized and have not yet had the definite outcome.

2.2. Cardiovascular manifestations of COVID-19

2.2.1. Acute myocardial injury

Acute myocardial injury is the most commonly described CV complication in COVID-19 (Table 1). Different reports have used different definitions for acute myocardial injury, including rise in cardiac enzymes (different biomarkers and cut-offs) and/or electrocardiographic abnormalities. However, an elevation of high-sensitivity cardiac troponin I (cTnI) above 99th percentile upper reference limit is the most commonly used definition.Table 1

The overall incidence of acute cardiac injury has been variable but roughly 8–12% of the positive cases are known to develop significant elevation of cTnI [10]. The aforementioned meta-analysis of the Chinese studies [4] reported 8% incidence of acute cardiac injury whereas another study including only those patients who had had a definite outcome (death or discharge from hospital) reported 17% incidence of cTnI elevation [5]. Regardless of the actual incidence, acute cardiac injury has been consistently shown to be a strong negative prognostic marker in patients with COVID-19 [5,6,8]. The patients admitted to ICU or having severe/fatal illness have several-fold higher likelihood of troponin elevation. In contrast, the incidence of elevated troponin has been very low (only 1–2%) in patients having mild illness not requiring ICU admission.

Any of the mechanisms described above can lead to acute cardiac injury and rise in cardiac troponins in patients with COVID-19. The relative role of these different mechanisms has not been described but direct (i.e. non-coronary) myocardial injury due to viral myocarditis or the effect of systemic inflammation appear to be the most common mechanisms. These observations are supported by a previous autopsy study in patients who had died due to SARS during the Toronto SARS outbreak [11]. In this study, the viral ribonucleic acid was detected in 35% of the autopsied human heart samples, providing evidence for direct myocardial injury by the virus.

No study has described the incidence of ST-segment elevation myocardial infarction in COVID-19, but it appears to be low. Similarly, the incidence of left ventricular systolic dysfunction, acute left ventricular failure and cardiogenic shock have also not been described. Only one Chinese study reported incidence of heart failure in COVID-19 patients [5]. Heart failure had occurred in 52% of the patients who subsequently died and in 12% of the patients who were discharged from the hospital.

2.2.2. Arrhythmias

Both tachy- and brady-arrhythmias are known to occur in COVID-19. A study describing clinical profile and outcomes in 138 Chinese patients with COVID-19 reported 16.7% incidence of arrhythmia [8]. The incidence was much higher (44.4%) in those requiring ICU admission as compared to those not requiring ICU admission (8.9%). The type of arrhythmia was not described.

2.2.3. Potential long-term consequences

COVID-19 has emerged only a few months ago and it is too early to predict long-term outcome of the patients who recover from this illness. However, some important messages can be gleaned from previous experiences with SARS, caused by SARS-CoV which shares considerable similarity with SARS-CoV-2. It was reported that among patients who had recovered from SARS, 68% continued to have abnormalities of lipid metabolism at 12-years follow-up; CV abnormalities were present in 40% and altered glucose metabolism in 60% [12]. Similar findings have also been reported in patients recovering from other respiratory tract infections [13]. Considering this, careful follow-up of those recovering from the current COVID-19 would be important to understand the long-term impact of this illness and also to protect these patients from future CVD.

2.3. Management implications

The overall management principles for patients presenting with COVID-19 who develop CV complications or who have pre-existing CVD are same as for any other patient without COVID-19. However, there are a few important points that need consideration-

1. As caregivers, it is our utmost responsibility to protect ourselves from getting infected while managing these patients. Therefore, all heathcare personnel engaged in the care of COVID-19 patients must observe necessary precautions at all times. All of them should be trained in donning, usage, and doffing of the personal protective equipment in accordance with the existing practice guidelines.
2. The hospital systems need to ensure preparedness for dealing with large volume of COVID-19 patients, many of whom would need ICU care and/or acute cardiac care. Appropriate protocols for rapid diagnosis, triage, isolation, and management of COVID-19 patients with CV complications should be developed and well-rehearsed. Rapid triaging and management of these patients is crucial, not only to allow efficient utilization of healthcare resources but also to minimize exposure to caregivers. There are already reports highlighting delays in delivering acute cardiac care due to extra precautions that need to be observed in view of COVID-19 [14]. Efforts should be made to minimize such delays.
3. Strong emphasis should be placed on avoiding unwarranted diagnostic tests (e.g. cardiac troponin, echocardiography, etc.) in these patients. This is required to minimize unwarranted downstream diagnostic/therapeutic procedures which would further strain the already stretched healthcare resources and would also subject caregivers to added risk of exposure to the infection. The American College of Cardiology has released an advisory discouraging random measurement of cardiac biomarkers such as troponins and natriuretic peptides [15]. It urges all the clinicians to reserve these assays for circumstances in which they would actually meaningfully add to the management of the patients with COVID-19. The American Society of Echocardiography has also issued a similar advisory regarding the use of echocardiography in these patients [16].
4. The individual hospitals may also have to reconsider risk-benefit ratio of primary percutaneous intervention vs fibrinolysis in patients with COVID-19 who present with ST-segment elevation myocardial infarction.
5. There has been a concern regarding the safety of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) during the ongoing COVID-19 pandemic. These agents upregulate expression of ACE2 in various tissues, including on cardiomyocytes [17]. Since SARS-CoV-2 binds to ACE2 to gain entry into human cells, there is a potentially increased risk of developing COVID-

19 or developing more severe disease in patients who are already on background treatment with ACEi/ARB. However, to date, no experimental or clinical data have emerged to support these concerns. At the same time, the risks of discontinuing these therapies are well known. Therefore, several leading professional societies have strongly urged to not discontinue clinically-indicated ACEi/ARB therapy in the event the patient develops COVID-19 [18,19].

6. Clinicians caring for these patients also need to be fully aware of the potential CV side-effects of various therapies used for treating the viral infection. Additionally, various anti-retroviral drugs have significant interactions with cardiac drugs, which need to be considered and appropriate dose modification done. More recently, chloroquine/hydroxychloroquine and azathioprine have been proposed as potential therapeutic options, based on preliminary evidence [20]. Both these drugs are known to prolong QT interval and due caution must be exercised when prescribing these agents. Their combination is best avoided and even when using chloroquine/hydroxychloroquine alone, daily electrocardiogram for monitoring QT interval is warranted, esp. in patients with hepatic or renal dysfunction and in those receiving another drug with potential to prolong QT interval.

3. Summary and future directions

Although respiratory illness is the dominant clinical manifestation of COVID-19, the shear burden of the illness implies that a large number of patients with COVID-19 would present with pre-existing CVD or develop new-onset cardiac dysfunction during the course of the illness. Considering this, the current understanding about the interplay between CVD and COVID-19 is grossly inadequate. It is therefore highly desirable that the future studies on COVID-19 specifically describe the incidence, mechanisms, clinical presentation and outcomes of various CV manifestations in these patients. The diagnostic and therapeutic challenges posed by the concurrence of these two illnesses also need to be adequately studied.

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