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Major cardiac concerns in therapy and vaccinations for COVID-19

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ABSTRACT

The necessity and impact of SARS-CoV-2 on the world's health have led to the development and production of practical and useful vaccines for this deadly respiratory virus. Since April 2020, a vaccine for the virus has been developed. Given that comorbidities such as diabetes, hypertension, and cardiovascular disease are more prone to viruses and the risk of infection, vaccines should be designed to protect against high-risk respiratory illnesses. In this review, we discussed the cardiovascular alteration in SARS-CoV-2 treatment, and we also reviewed the vaccination information and studies that have been done to primary considerations for cardiac patients.

1. Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in late December 2019. Since then, COVID-19 has spread rapidly worldwide and has become a global pandemic, with a remarkable effect on public health and social and economic activities [1]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2], which is a member of the genus *Betacoronavirus* like the two other coronaviruses that have caused pandemic diseases (severe acute respiratory syndrome coronavirus (SARS-CoV) [3] and Middle East respiratory syndrome coronavirus (MERS- CoV)) [4]. SARS-CoV and MERS-CoV, SARS-CoV-2 cause respiratory infection, leading to viral pneumonia and acute respiratory distress syndrome (ARDS) in some patients [5].

However, in addition to respiratory symptoms, uncontrolled SARS-CoV-2 infection can trigger a cytokine storm. Pro-inflammatory cytokines and chemokines such as tumor necrosis factor- α, IL-1β and IL-6 are overproduced by the immune system, resulting in multiorgan damage [6]. Furthermore, COVID-19 causes coagulation abnormalities in a substantial proportion of patients [7], leading to thromboembolic events [8]. The genomic sequence [9]and viral protein structure [10] of SARS-CoV-2 have been studied intensively since its emergence. Understanding the biological features of the virus will contribute to the development of diagnostic tests, vaccines, and pharmacological therapies and can further our knowledge of tissue tropism [11]. Early clinical data indicate that both the susceptibility to and the outcomes of COVID-19 are strongly associated with cardiovascular disease (CVD) [12]. A high prevalence of pre-existing CVD has been observed among patients with COVID-19, and these comorbidities are associated with increased mortality [13]. Furthermore, COVID-19 seems to promote the development of cardiovascular disorders, such as myocardial injury [14], arrhythmias, acute coronary syndrome (ACS), and venous thromboembolism [15].

Children with COVID-19 have also been reported to develop hyperinflammatory shock with features akin to Kawasaki disease, including cardiac dysfunction and coronary vessel abnormalities [16]. Together, this data indicate bidirectional interaction between COVID-19 and the cardiovascular system, but the mechanisms underlying this interaction remain elusive. The high burden of systemic inflammation associated with COVID-19 has been proposed to accelerate the development of subclinical disorders or cause de novo cardiovascular damage [17]. ACE2, an essential surface protein for virus entry and part of the renin-angiotensin–aldosterone system (RAAS), is also thought to be involved in this interaction based on findings from animals [18].

The first mass vaccination program started in early December 2020, and as of 15 February 2021, 175.3 million vaccine doses have been administered. At least 7 different vaccines (3 platforms) have been administered. WHO issued an Emergency Use Listing (EULs) for the

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Pfizer COVID-19 vaccine (BNT162b2) on 31 December 2020. On 15 February 2021, WHO issued EULs for two versions of the AstraZeneca/Oxford COVID-19 vaccine manufactured by the Serum Institute of India. WHO is on track to EUL other vaccine products through June, 2021 [19]. At the same time, more than 200 additional vaccine candidates are in development, of which more than 60 are in clinical development. COVAX is part of the ACT Accelerator, which WHO launched with partners in 2020. COVAX, the vaccines pillar of ACT Accelerator, was convened by CEPI, Gavi, and WHO [20].

2. The cardiovascular system and COVID-19

2.1. Underlying cardiovascular comorbidities

CVD is common comorbidity observed in patients infected with SARS or MERS [21] (with a prevalence of 10% and 30%, respectively) [22]. A series of reports on the clinical characteristics of patients with COVID-19 have also described similar findings [23]. Early reports from China found that CVD and its risk factors, such as hypertension and diabetes mellitus, were common pre-existing conditions in patients with COVID-19. Still, the definition of CVD used in each study was vague [24]. In an early report from Wuhan involving 41 patients who were hospitalized with COVID-19 by 2 January 2020, the prevalence of any comorbidity was 32%, and the most common underlying diseases were diabetes (20%), hypertension (15%), and other CVDs (15%) [25]. The high prevalence of these comorbidities was confirmed in subsequent studies [26].

2.2. Diverse cardiovascular manifestations

Although the predominant clinical manifestation of COVID-19 is viral pneumonia [27], COVID-19 can also cause cardiovascular disorders such as myocardial injury, arrhythmias, ACS, and thromboembolism. Some patients who present without the typical symptoms of fever or cough have cardiac symptoms as the first clinical manifestation of COVID-19 [28]. Myocardial injury during COVID-19 is independently associated with high mortality [29]. Furthermore, a possible link between COVID-19 and a Kawasaki disease-like syndrome has been described in children [30].

2.3. Acute coronary syndrome

As with other infectious diseases, including SARS and influenza, COVID-19 can trigger ACS [32]. In early studies from China, a small proportion of patients with COVID-19 presented with chest pain on admission to the hospital, but the chest pain characteristics were not described [33].

2.4. Myocardial injury and myocarditis

As evidenced by elevated cardiac biomarkers, including Troponin I and N-terminal pro brain natriuretic peptide or electrocardiogram abnormalities, the acute myocardial injury was observed in 7–20% of patients with COVID-19 in early studies in China [28]. The presence of myocardial injury was associated with a significantly worse prognosis [31].

2.5. Arrhythmias and sudden cardiac arrest

Arrhythmias and sudden cardiac arrest are common manifestations of COVID-19. Heart palpitations have been reported to be the main presenting symptom of COVID-19 in patients without fever or cough [37]. Elevated levels of troponin T were more likely to develop malignant arrhythmias, such as ventricular tachycardia and fibrillation, than those with normal levels of troponin T (12% versus 5%). In-hospital and out-of-hospital sudden cardiac arrests have also been reported in patients with COVID-19 [38]. However, the exact contribution of COVID-19 to cardiac arrhythmias remains unclear, given that arrhythmias, such as atrial and ventricular tachycardia and fibrillation, can be triggered by myocardial injury or other systemic causes such as fever, sepsis, hypoxia, and electrolyte abnormalities [39]. Furthermore, patients with advanced COVID-19 are often treated with antiviral medications and antibiotics known to induce arrhythmias in some patients [40].

2.6. Heart failure

Acute myocardial injury and ACS triggered by COVID-19 can also aggravate pre-existing heart disease or provoke contractile dysfunction. In the advanced stages of COVID-19 [34], the immune system's response to infection might trigger the development of stress-induced cardiomyopathy or cytokine-related myocardial dysfunction, as with sepsis-associated cardiac dysfunction [35].

COVID-19 primarily causes respiratory symptoms and viral pneumonia with bilateral, peripheral, and lower lung distribution. Pulmonary edema observed in these patients, usually accompanied by ARDS, is mainly regarded as non-cardiogenic. However, given that approximately 25% of patients hospitalized with COVID-19 develop heart failure, the potential contribution of pulmonary congestion by heart failure should be taken into consideration for patients with COVID-19-related respiratory failure to validate this involvement [36].

2.7. ACE2 and cardiovascular manifestations

The mechanisms underlying the development of COVID-19-related cardiovascular injury are not known. ACE2 expression is considered one of the significant factors involved in the biological mechanism underlying tissue-specific infection. SARS-CoV-2 infection is triggered by binding viral S protein to human ACE2, whereas TMPRSS2 induces S protein priming. The interaction between S protein [41]and ACE2 has gained much research interest, given that ACE2 is known to have crucial roles in both the cardiovascular system and the immune system [42]. ACE2 is a part of the RAAS and is involved in developing diabetes, hypertension, and heart failure. ACE2 is highly expressed at the tissue level in the lungs, kidneys, heart, and blood vessels [42]. According to bulk RNA sequencing data in the Genotype-Tissue Expression (GTEx) project V8, the expression of ACE2 in the heart and coronary arteries is even higher than in the lungs [43]. At the single-cell level, ACE2 is highly expressed in pericytes of adult human hearts [44]. Single-cell RNA sequencing data have also revealed that cardiomyocytes (especially those in the right ventricle) express ACE2 at a lower level than pericytes and that neither pericytes nor cardiomyocytes express TMPRSS2 [45].

However, both cell types have a high expression of cathepsin B and cathepsin L, facilitate S protein priming, and promote entry of the virus into the cell via the endocytic pathway. Therefore, SARS- CoV-2 might be capable of directly infecting multiple cardiovascular cell types, including cardiomyocytes, endothelial cells, and pericytes. Notably, the expression of ACE2 is not in itself sufficient for entry of the virus into a cell, and the efficiency of viral replication and release might also have a role in host cell infection. To date, clinical evidence of direct viral infection of cardiomyocytes has not been found. Given that myocarditis related to SARS- CoV-2 infection is rare [33], the interaction between SARS-CoV-2 and ACE2 might affect the cardiovascular system indirectly [17]. Genome-wide association studies would help to identify novel pathways involved in SARS- CoV-2 pathogenesis [46].

2.8. Cardiovascular effects of antiviral drugs

At present, many research teams worldwide are focused on developing drugs for the prevention and treatment of COVID-19. Of note, the development and testing of new medications are time-consuming processes [47] and not a viable strategy during this COVID-19 pandemic.

Table 1
Adverse cardiovascular effects of potential drugs to treat COVID-19 [6].

Drug	Mechanism of action	Cardiovascular adverse effects
Inhibitors of endocytosis		
Chloroquine and hydroxychloroquine	Blockade of virus entry by multiple mechanisms	QT interval prolongation
Umifenovir	Inhibition of S protein–ACE2interaction and membrane fusion	Not common, but limited clinical data
Inhibitors of synthesis of non-structural proteins		
Lopinavir–ritonavir	Inhibition of 3- chymotrypsin-like protease	Atrioventricular block and cytochrome P450 3A4- related drug-drug interaction
Inhibitors of viral RNA replication		
Favipiravir	Inhibition of RdRP	Not common, but limited clinical data
Remdesivir	Inhibition of RdRP	Not common, but limited clinical data
Ribavirin	Inhibition of RdRP	Not common
Others		
Azithromycin	Macrolide antibiotic; used in combination with chloroquine or hydroxychloroquine	QT interval prolongation
Tocilizumab	IL-6 inhibition	Hypertension

ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; RdRP, RNA-dependent RNA polymerase; S protein, spike protein.

Drug repurposing, in which existing medications that have already been approved for a disease are tested for a new condition [48], is currently the primary approach in searching for new drugs for COVID-19 [49]. However, some drugs under investigation have known or unknown cardiovascular adverse effects [50] or might be involved in drug-drug or drug-disease interactions (Table 1).

3. Recommended Vaccines for COVID-19

Currently, researchers are working hard to find an effective vaccine to treat the COVID-19, but there are many scientific and logistical challenges involved. One of the most important of these challenges is finding out how the immune system works with both the pathogen and the vaccine itself and the vital strategies for producing a safe and effective vaccine [49]. According to the World Health Organization (WHO), 5–200 candidate vaccines for COVID-19 in clinical and pre-clinical evaluation, respectively. Table 2 showing WHO Recommended Vaccines for SARS-CoV-2 [20]. Many platform cases of vaccines against SARS-CoV-2 are in the clinical assessment, including nonreplicating viral vector, recombinant ChAdOx1 adenoviral, and recombinant replication peptide antigen inactivated, DNA, and mRNA.

Scientists also need to know whether the vaccine, like previous vaccines, stimulates and strengthens the immune system. Contrary to current evidence, the vaccinated people after virus exposure showed a higher immune response than those who have not been vaccinated [51]. The following might be cited despite all the above efforts, including the recommended immunizations for COVID-19. People with heart disease or stroke, or for that matter, risk factors for heart disease and stroke, are at much greater risk from the virus than they are from the vaccine.

4. Current vaccine landscape

The US Food and Drug Administration has approved two vaccines for emergency use made by Pfizer-BioNTech and Moderna. Both are two-dose series with excellent efficacy. In Phase 3 trials, the Pzifer-BioNTech vaccine (n = 43,449) conferred 95% protection, and the Moderna vaccine (n = 30,420) 94.1% protection from the infection. Equally important is that subjects who become infected with COVID-19 despite being fully vaccinated experience substantial protection from severe illness [52]. Pfizer-BioNTech is currently approved in persons ≥16 years old and Moderna ≥18 years old.

Both vaccines are highly reactogenic, eliciting a robust immune response. Minor side effects are common, particularly after the second dose, and include injection site pain, fever, headache, chills, myalgia, and fatigue. Severe reactions are uncommon, though available data at this time can only speak towards short-term safety issues [53]. Vaccination of the population at large has the potential to reveal previously unknown rare side effects [53]. An anaphylactic reaction is sporadic, with rates reported at 4.7 cases per million doses for the Pfizer-BioNTech vaccine and 2.5 cases per million doses for the Moderna vaccine. Patients with a prior severe allergic reaction to any vaccine components should not receive the COVID-19 vaccine. Misconceptions about the vaccines should be addressed and may include concerns over the vaccination causing COVID-19 infection and that receiving the vaccine may worsen a patient's underlying heart disease. Patients with a history of COVID-19 infection should also be educated on the necessity of vaccination for potentially longer-lasting immunity.

The American College of Cardiology (ACC) recommends that acquired cardiovascular disease and adult congenital heart disease (ACHD) patients at an advanced, decompensated physiologic stage be considered among the highest risk cardiac patients and prioritized for vaccination. In a single-center cohort of 53 CHD patients with COVID-19 infection (10 pediatric, 43 adults), advanced physiologic stage, but not increasing complexity of anatomy, was associated with an increased odds of having a moderate or severe illness (OR 19.38, p = 0.002) [53]. Thus, a single ventricle patient post-Fontan palliation with excellent intracardiac hemodynamics may fare better than a repaired tetralogy of Fallot patient with significant valve regurgitation or profound ventricular dysfunction.

There are still few vaccines tested in phase 2 or 3 studies. However, the results are positive and impactful, both in terms of safety and effectiveness. It is worth mentioning that the vaccines supported by Pfizer [54], Moderna [55], and AstraZeneca [56] have included the elderly, cardiac patients, diabetics, severely obese individuals, Afro-descendants, and Latinos. And, despite their relatively small number, that inclusion allows us to infer safety and efficacy for cardiac patients. The adverse effects observed were local but less common in the elderly. The cardiovascular effects observed, such as hypertension, bradycardia, tachycardia, atrial fibrillation, ACS, and pulmonary thromboembolism, had a frequency lower than 0.1% and were similar in those who received the vaccines received placebo [57].

5. Conclusion

COVID-19 is an unprecedented challenge to the health of many individuals and the healthcare system of many countries. Current research and development of vaccines have led to much progress. With further testing, they may halt the spread of morbidity and mortality caused by COVID-19 and its complications on cardiovascular disease and care provision. From a biological perspective, we have summarized our present SARS-CoV-2 understanding and emphasized the interaction between the viral S protein and human ACE2. We provided an overview of the clinical findings related to the effects of COVID-19 on the cardiovascular system. Finally, we addressed the possible link between

Table-2
Availble Vaccines for SARS-CoV-2 (A-Z order).

S. No	Name of Vaccine	Type of Vaccine	Manufacturer
1	Ad26.COV2.S	Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein	Janssen Pharmaceuticals, Netherlands and Johnson & Johnson, USA
2	AZD1222	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	SKBIO- AstraZeneca
3	BNT162b2/ COMIRNATY Tozinameran (INN)	Nucleoside modified mRNA	Pfizer
4	COVAXIN	SARS-CoV-2 Vaccine, Inactivated (Vero Cell	Bharat Biotech, India
5	Covishield (ChAdOx1_nCoV19)	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	Serum Institute of India
6	mRNA-1273	mRNA-based vaccine encapsulated in a lipid nanoparticle (LNP)	Moderna
7	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV)	Inactivated, produced in Vero cells	Sinopharm, China
Clinical trials-Vaccines			
8	Ad5-nCoV	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	CanSino Biologics, Chinese
9	EpiVacCorona	Peptide antigen	Vector State Research Center of Virology and Biotechnology, Russian
10	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Inactivated, produced in Vero cells	Sinopharm, China
11	NVX-CoV2373/ Covovax	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant	Novavax, USA
12	Recombinant Novel Coronavirus Vaccine (CHO Cell)	Recombinant protein subunit	ZhifeiLongcom, China
13	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	Inactivated	IMBCAMS, China
14	SCB-2019	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein
15	Soberana 01,Soberana 02 Soberana Plus	SARS-CoV-2 spike protein conjugated chemically to meningococcal B or tetanus toxoid or Aluminum	BioCubaFarma, Cuba
16	Sputnik V	Human Adenovirus Vector-based Covid-19 vaccine	Gamaleya Research Institute of Epidemiology and Microbiology, Russian
17	Zorecimeran (INN)	mRNA-based vaccine encapsulated in a lipid nanoparticle (LNP)	CureVac, German

common cardiovascular drugs and susceptibility to COVID-19 and the potential cardiovascular effects of drugs used to treat COVID-19. Our review supports the value of COVID-19 vaccines in reducing the burden of the disease in patients with preexisting cardiovascular conditions.

Authors contribution

Conceptualization; Bojjibabu Chidipi. Drafting manuscript; Syam Sundar Junapudi, Sunil Junapudi, Kishore Ega, and Bojjibabu Chidipi.

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Declaration of competing interest

The authors declare no conflict of interest.

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