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COVID-19 and the cardiovascular system: An update

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ABSTRACT

As COVID-19 continues to cause an increasing number of deaths worldwide, it is important that providers stay abreast with new research related to the pathophysiology of COVID-19 disease presentation states and clinical management. It is now well recognized that COVID-19 affects extrapulmonary organs, particularly the cardiovascular system. For example, cardiogenic shock has been increasingly observed in patients with COVID-19, owing to the various mechanisms involved and the affinity of the SARS-CoV-2 virus to cells comprising the cardiovascular system. In this review, we have briefly discussed the link between the cardiovascular system and COVID-19 infection, focusing on underlying mechanisms including but not limited to cytokine storm, direct virus-induced myocarditis, and ST-elevation myocardial infarction leading to cardiogenic shock. We have highlighted the cardiovascular risk factors associated with disease prognostication in COVID-19 patients. We have also briefly discussed vasopressors and inotropes used for treating shock and presented their mechanism of action, contraindications, and side effects in the hopes of providing a quick reference to help the provider optimize management of COVID-19 patients presenting with cardiovascular complications such as shock.

Key Indexing Terms: COVID-19; Coronavirus; Cardiovascular complications; Myocarditis; Vaccine; SARS-CoV-2; Shock; Vasopressor; Inotropes. **[Am J Med Sci 2022;364(2):139–147.]**

INTRODUCTION

The Coronavirus disease-19 (COVID-19) pandemic continues to wreak havoc, causing an increasing number of deaths worldwide since being first reported in Wuhan, China.[1] The death toll caused by the SARS-CoV-2 virus as of January 1st 2022 has since surpassed 824,000 in the USA despite large strides made in understanding the pathophysiology, management, and prevention of spread.[2] While the SARS-CoV-2 virus is known principally for its pulmonary effects, including pneumonia and acute respiratory distress syndrome (ARDS), other extrapulmonary manifestations have been reported. In fact, cardiovascular, hematologic, gastrointestinal and hepatobiliary, renal, endocrinologic, neurologic, and dermatologic systems have been reported to be affected by the virus via direct or indirect means.[3,4] Therefore, individuals affected by COVID-19, especially the severely ill, can present with multi-organ involvement/failure requiring prompt intervention. For these severely ill COVID-19 patients known to have a high mortality rate, it is not uncommon that their presentation to the intensive care unit will involve shock of a specific or mixed type.[5-7] Various mechanisms responsible for shock in COVID-19 patients, such as cytokine storm, have been proposed[8,9]; therefore, the provider must keep abreast and must have a clear understanding of these mechanisms as new studies emerge. In this review, we will focus on the cardiovascular complications associated with COVID-19 while highlighting how they can culminate into shock. We will discuss how severely ill COVID-19 patients can be managed by providing a summary of the different inotropes and vasopressors in the hopes that it will serve as a quick guide for the provider.

CARDIOVASCULAR MANIFESTATIONS OF COVID-19 AND UNDERLYING PATHOPHYSIOLOGY

The SARS-CoV-2 virus is known to cause direct myocardial injury and induce arrhythmias and acute coronary syndromes (ACS) leading to acute heart failure and shock.[10-13] Specifically, injury to the myocardium as evidenced by elevated cardiac biomarkers has been reported in up to 30% of hospitalized COVID-19 patients and up to 55% in those with pre-existing cardiovascular disease. Interestingly but not surprisingly, the magnitude of troponin elevations in these hospitalized patients is associated with poorer outcomes.[14-17]

Why is the heart particularly vulnerable to the SARS-CoV-2 virus? The reason is thought to be related to the mechanism utilized by the virus to gain cell entry. The

angiotensin-converting enzyme 2 (ACE2) receptor, used by the virus to gain cellular access, is highly expressed in cardiovascular tissues, including cardiac myocytes, endothelial cells, fibroblasts, and smooth muscle cells.[18-21] Thus, direct viral interaction through these receptors supports a direct cytotoxic effect of the virus on cardiomyocytes. Also supporting this is the finding that viral particles have been isolated from autopsied heart specimens, although the majority of recent reports have failed to demonstrate such particles in autopsied specimens while noting inflammatory infiltrates in the myocardium.[22-24] For example, in one study in which autopsies were performed in 21 patients with COVID-19, myocarditis was observed in three cases (14%) while various other forms of myocardial injury were also observed, including widespread increased interstitial macrophage infiltration of the myocardium (86% of cases).[25] However, no clear associated myocyte injury involving both ventricles was reported. Also, the authors did not find viral particles in cardiac macrophages either. This finding supports widespread myocardial inflammation or myocarditis, characterized by inflammatory infiltrates and injury to heart tissue, without ischemic insult as another plausible mechanism. [26,27] However, it is difficult to estimate the exact prevalence of myocarditis among COVID-19 patients partly because early reports lacked diagnostic modalities to assess myocarditis. Some studies have reported that up to 7% of COVID-19 −related deaths were secondary to myocarditis although nearly all the information about myocarditis in these patients came from case reports or small series.[28-39] For example, Sawalha et al[29] identified a total of 14 COVID-19 cases with myocarditis/myopericarditis, reporting a male predominance (58%), with a median age of 50.4 years. Of note, most patients did not have a previously identified comorbid condition (50%). Recovery of cardiac structure and function has been noted; for example, fulminant myocarditis with elevated troponin and improvement in left ventricular function following treatment with antivirals, intravenous immunoglobulin, and steroids, and subsequent normalization of troponins have been reported.[40-42]

As briefly mentioned above, since the SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) receptor, an important question is whether routine use of angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) in COVID-19 patients is protective or increases susceptibility to the virus, especially in patients with hypertension, heart failure, and/or diabetes, who are overrepresented among critically ill COVID-19 patients. So far, there is no evidence to support an association between ACEi and ARBs use and COVID-19 severity, while some other studies have shown potential benefits.[43-48] Therefore, currently, the routine discontinuation of these medications is not recommended based on recommendations by the European society of cardiology and the American College of Cardiology.

Cardiac arrhythmias, including new-onset atrial fibrillation, heart block, and ventricular arrhythmias, are also prevalent in COVID-19 patients, occurring in 17% of hospitalized patients and up to 44% of ICU patients as first reported in a study of 138 patients from Wuhan, China. These arrhythmias have since been recognized as common features of COVID-19 and are associated with poorer outcomes.[49-51] Malaty et al have summarized more recent studies discussing the incidence and treatment of arrhythmias secondary to COVID-19 and the reader is thus directed there for more information.[52] Non-valvular atrial fibrillation (NVAF) seems to be the most common arrhythmia encountered in COVID-19 patients and COVID-19 is increasingly being postulated as an independent risk factor for stroke in patients with NVAF.[53,54] Of note, although the exact mechanistic pathways leading to arrhythmias remain unknown at large, plausible mechanisms, as discussed by Siripanthong et al, include direct injury to cardiomyocytes disrupting electrical conduction, pericardial edema affecting electrical conduction, ischemia disrupting electrical conduction, re-entrant arrhythmias due to myocardial fibrosis or scars, and arrhythmias caused by proinflammatory cytokines predisposing to arrhythmogenicity.[55] In a multicenter New York City cohort, of the 4,250 patients with COVID-19, 6% were noted to have a prolonged QTc (i.e., corrected QT; >500 ms)[5] and in a different cohort of 393 patients with COVID-19, atrial arrhythmias were more common among patients requiring mechanical ventilation than those who did not (17.7% versus 1.9%).[56] In the New York City cohort, prolongation of QT could have been iatrogenic from the use of azithromycin and hydroxychloroquine at that time.[5]

Other indirect mechanisms leading to myocardial damage include stress-mediated myocardial dysfunction that could result from hypertensive emergency, tachycardia-induced cardiomyopathy, myocardial stunning after prolonged hypotension leading to supply-demand mismatch (i.e., type 2 MI), and hypoxia-induced myocardial damage caused by ARDS secondary to COVID-19. COVID-19 patients also have an exaggerated risk for myocardial infarction given that COVID-19 is a hypercoagulable state that can lead to widespread thrombosis in the arterial and venous systems resulting in ischemic injury and venous thromboembolism that can cause significant heart strain culminating to fatal complications. Thrombosis is a result of endothelitis triggered by direct interaction of viral particles with the endothelium or a result of hyperviscosity induced by the heightened proinflammatory state of COVID-19.[57-60]

FACTORS INCREASING THE RISK FOR CARDIOVASCULAR COMPLICATIONS IN COVID-19

Cardiovascular risk factors can play a crucial role in identifying patients vulnerable to developing cardiovascular manifestations of COVID-19. The reader is directed

to the review by Shifi et al for a detailed review of these risk factors.[12] In brief, hypertension and diabetes have been noted to be among the most common of these risk factors. Wu and McGoogan found that when the case fatality rate (CFR) of COVID-19 was high in critically ill patients, those with pre-existing conditions experienced an even higher rate – 10.5% for those with cardiovascular disease, 7.3% for diabetes, and 6.0% for hypertension.[61] These pre-existing conditions have also been shown to correlate with mortality. For example, when 150 COVID-19 patients were analyzed, Shafi et al found that hypertension, diabetes, pre–existing cardiovascular disease (CVD), and cerebrovascular disease were responsible for 43%, 18%, 19%, and 10% of all deaths, respectively.[12] Thirty-nine percent of these deaths were attributed to heart failure or respiratory failure. The studies by Zhou et al and Shi et al also highlighted the association of hypertension and diabetes as important risk factors.[14,62] In a separate retrospective study conducted in Italy involving 188 COVID-19 patients admitted to the ICU, hypercholesterolemia was found to be another significant comorbidity predicting poorer outcomes involving cardiovascular implications.[63] All of the 188 patients admitted to the ICU had hypercholesterolemia, indicating the importance as a risk factor. The commonest risk factors in this cohort associated with an adverse cardiovascular complication included hypertension (27%), CVD (12.1%), and diabetes (11.5%). Guo et al found that elevated troponin levels were associated with more frequent arrhythmias and higher levels of other cardiac biomarkers.[14]

Once the SARs-CoV virus enters myocytes, viral inclusions, and inflammatory cells such as macrophages, neutrophils, and lymphocytes follow.[64] This viral-mediated infiltration can cause myocardial edema or myocarditis coupled with necrosis, resulting in dilated cardiomyopathy and heart failure.[65,66] Studies have shown that myocarditis is present in up to 30% of patients with COVID-19 and those with myocarditis have poorer prognoses.[67,68] Of note, the development of heart failure depends on comorbidities, age, and the severity of cardiac involvement, as well as other factors. As summarized by Shafi et al, based on all studies, approximately 8% of patients developed heart failure/cardiogenic shock as a complication of COVID–19.[12] The first of such reports on cardiogenic shock in otherwise healthy males with a diagnosis of COVID-19 suggest that shock is induced by direct viral-mediated myocardial injury.[69] Patients presented with hyperinflammatory biomarker profiles and multiorgan dysfunction including biventricular failure and responded to treatment with methylprednisolone. In a different report, Fried et al reported some of the various cardiovascular presentations of COVID–19 in which three out of four cases developed cardiogenic shock.[70] They highlighted how swift recognition of cardiogenic shock in these cases was crucial for appropriate clinical decision making. Tavazzi et al described the first case of acute cardiac injury directly linked to myocardial localization of the SARS-CoV-2 virus in a 69-year-old patient who presented with cardiogenic shock.[22] Chnonyang et al demonstrated cardiomyocyte infection with SARS-CoV-2 virus in a patient presenting with cardiogenic shock.[71] In one retrospective study carried out in Wuhan, China, heart failure was ranked as the fourth most common outcome of COVID-19.[62] In another study, 49% of all deaths were attributable to heart failure in individuals who had no prior history of cardiovascular diseases.[72] Several other case reports of COVID–19 patients presenting with cardiogenic shock have since been reported.[73-76] The mechanism leading to this outcome is multifactorial and can be linked to sepsis, respiratory failure and ARDS, direct cardiac injury, ACS caused by coronary thrombosis due to COVID-19 associated coagulopathy, and direct injury to the myocardium by the SARS-CoV-2 virus.

The heightened proinflammatory state in COVID-19 also plays a role in myocardial damage. Pro-inflammatory cells release cytokines such as Monocyte chemoattractant protein-1 (MCP-1), a major cytokine noted to increase significantly after COVID-19 onset. MCP-1 is a major regulator of monocyte/macrophage migration to the site of SARS-CoV-2 infection.[77] The accumulation of monocytes/macrophages around viral inclusions in the myocardium can disrupt heart function either mechanically or electrically. Interleukin-1β (IL-1β), another key regulator of inflammatory response, is pivotal in the etiology of COVID-19. IL-1β can stimulate the release of IL-21, IL-17, and IL-22 which mediate cell proliferation and differentiation that may contribute to myocardial thickening leading to cardiomyopathy. Tumor necrosis factor-alpha (TNF-α) secreted by macrophages, neutrophils, mast cells, and cardiomyocytes can also promote cellular proliferation and myocardial thickening.[78]

TREATMENT CONSIDERATIONS OF COVID-19 PATIENTS PRESENTING WITH CARDIOVASCULAR COMPLICATIONS CULMINATING TO SHOCK

A firm comprehension of the pathophysiology of the cardiovascular complications in COVID-19 patients will aid in swiftly recognizing and targeting treatment of potentially fatal complications such as cardiogenic shock thereby prompting targeted management. Multiple etiologies underlie the different shock states, including cardiogenic, hypovolemic, distributive, obstructive, or mixed type, often encountered in COVID-19 patients (Figure 1). Irrespective of the underlying etiology, the hallmark of any type of shock in general and including COVID-19 patients is decreased organ perfusion culminating into multiorgan dysfunction and death. Quick recognition of shock decreases morbidity and mortality in hospitalized COVID-19 patients. Obstructive shock caused by a pneumothorax in ventilated patients or critically ill patients on high dose steroids, for example,

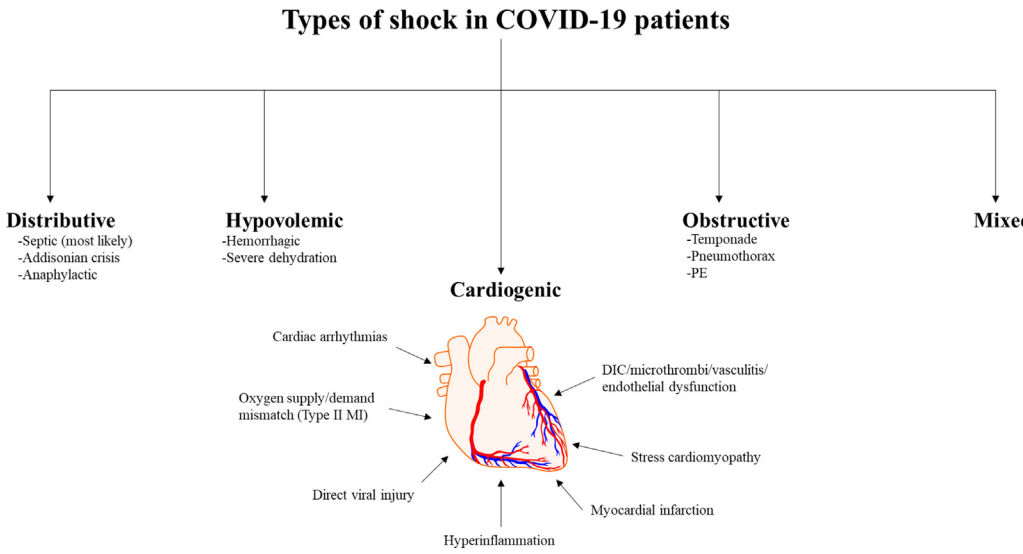

FIGURE 1. Types of shock. In COVID-19 patients, similar to non-COVID-19 patients, the cause of shock can be multifactorial, and different shock types can occur simultaneously. Cardiogenic shock can result from a variety of causes given the systemic nature of COVID-19. The cause of shock can also be iatrogenic; hemorrhage can result from anticoagulation therapy while pneumothorax can be caused by barotrauma or has been associated with high dose corticosteroids use.[101,102] The initial evaluation of critically ill COVID-19 patients supposedly in shock must take into consideration these potential causes.

warrants prompt decompression rather than treatment with vasoactive agents. Similarly, cardiogenic shock due to myocarditis/cardiomyopathy caused by cytokine storm may respond to anti-inflammatory treatments and monoclonal antibodies which are increasingly being added to the therapeutic regimens of COVID-19.[79-81]

Vasopressors and inotropes create vasoconstriction or increase cardiac contractility, respectively, in patients with shock leading to increased mean arterial pressure (MAP) and improved organ perfusion. A summary of vasopressors and inotropes used to increase MAP is summarized in Table 1. Some less commonly used medications which should be considered in circumstances where the goal MAP cannot be achieved despite the use of multiple vesopressors/inotropes have also been highlighted. The use of a mineralocorticoid/corticosteroid such as hydrocortisone should not be overlooked in cases of refractory shock as studies have shown that it is not unusual for critically ill patients to have relative adrenal insufficiency.[82-85]

Early revascularization, as demonstrated in the SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial, remains the most important treatment in managing cardiogenic shock caused by acute MI.[86] In severe COVID-19 cases with refractory shock, right ventricular failure, and extreme hypoxic lung injury, extracorporeal membrane oxygenation or other mechanical circulatory support such as Impella or intra-aortic balloon pump can be used.[87] In addition to these measures, other supportive management must be used concomitantly. For example, adequate fluid resuscitation whenever required and treatment with other adjunctive therapies such as ramdesevir and tocilizumab.

The comprehension of the hemodynamic principles and adrenergic and non-adrenergic receptor mechanisms are important to appropriately utilize vasoactive/ionotropic medications for shock management in COVID-19 patients. Carefully selecting these medications based on the desired pharmacologic effects that are matched to the patient's underlying pathophysiology of shock is likely to optimize hemodynamics, while reducing adverse effects and increasing overall survival. As highlighted, the relative hemodynamic effect of some agents can depend on the dose administered. Norepinephrine remains the reasonable first-line agent for different shock states, most notably septic shock. Whereas dobutamine is a reasonable first-line inotrope agent. We hope that this document will serve as a quick guide for all healthcare providers managing critically ill COVID-19 patients who may present with cardiogenic or other forms of shock.

Since the start of vaccination against COVID-19, disease severity and overall mortality related to complications have been greatly mitigated. Patients fully vaccinated against COVID-19 are very less likely to have severe symptoms leading to shock and ICU hospitalization. We anticipate that as the pool of vaccinated individuals continues to increase, the less we are to encounter patients with severe symptoms and complications. That notwithstanding, they have been reports of adverse effects, including cardiovascular complications such as myocarditis and pericarditis occurring predominantly in males after receipt of the second vaccine dose of any of the available COVID-19 vaccine.[88-90] Despite this, the Advisory Committee on Immunization Practices (ACIP) maintained that the benefits, i.e., prevention of COVID-19 disease and associated morbidity and mortality, far

Table 1.

Drug	Clinical Indication	Dose Range	Receptor Binding						Note on use in COVID-19 patients	Major Side Effects	Contraindications
			α1	β1	β2	DA	V1*	V2*			
Catecholamines											
Norepinephrine	Vasodilatory shock Cardiogenic shock	0.025 - 1 mcg/kg/min 0.05 - 0.4 mcg/kg/min	+++++	+++	++	N/A	N/A	N/A	Norepinephrine is the first-line drug. See Gubbi et al[91] for a discussion of the complex interplay between catecholamines and COVID-19	Hypertension and arrhythmias	No contraindications to its use in a life-threatening situation
Epinephrine	Vasodilatory shock Cardiogenic shock Anaphylactic shock Bradycardia	0.01 - 0.5 mcg/kg/min 0.01 - 0.5 mcg/kg/min 0.01 - 0.03 mg/kg 0.1 - 0.5 mcg/kg/min	+++++	++++	+++	N/A	N/A	N/A	Not the preferred initial agent in cardiogenic shock. See Gubbi et al[91] for a discussion of catecholamines and COVID-19	Arrhythmias and hypertension[92]	No absolute contraindications
Dopamine	Cardiogenic shock Bradycardia	5 - 15 mcg/kg/min** 5 -20 mcg/kg/min.	+++	++++	++	+++++	N/A	N/A	Not the preferred initial agent in cardiogenic shock. See Gubbi et al[91] for a discussion of catecholamines and COVID-19	Hypertension and arrhythmias	Pheochromocytoma and tachyarrhythmias[93].
Dobutamine	Cardiogenic shock Decompensated HF Bradycardia	Usual dosing range is 2 - 20 mcg/kg/min	+	+++++	+++	N/A	N/A	N/A	According to AHA and ACCF, doses >20 mcg/kg/min are not recommended in heart failure	Tachycardia, PVCs, and angina pectoris	Pheochromocytoma and tachyarrhythmias.[93]
Phenylephrine	Vasodilatory shock Post cardiac arrest	0.5 - 6 mcg/kg/min 0.5 - 2 mcg/kg/min	+++++	0	0	N/A	N/A	N/A	Not a first-line or second-line treatment for septic shock##	Hypertensive and reflex bradycardia[94]	No absolute contraindications
Isoproterenol	Cardiogenic shock Bradyarrhythmias Torsade de pointes	2 - 20 mcg/minute 2 - 10 mcg/min 2 - 10 mcg/min	0	++++++++++		N/A	N/A	N/A	May further reduce systemic vascular resistance	Paradoxical bradycardia, tachyarrhythmias, ventricular arrhythmias	Preexisting ventricular arrhythmias, cardiac glycoside overdose[95]
Phosphodiesterase inhibitors											
Milrinone	Decompensated HF with evidence of end-organ hypoperfusion$.	0.125 to 0.75 mcg/kg/min				N/A			Requires renal dose adjustment$	Ventricular and supraventricular arrhythmias and hypotension[96]	Hypersensitivity to milrinone
Others											
Vasopressin*	Vasodilatory shock	Initial: ≤0.03 units/min added to norepinephrine[97]			N/A		+++++	+++++	Use in addition to norepinephrine and titrate to the lowest effective dose. Caution with doses	Arrhythmias, hypertension decreased CO (at doses >0.4 U/min)[95]	Hypersensitivity to vasopressin

(*continued on next page*)

Table 1. (*continued*)

Drug	Clinical Indication	Dose Range	Receptor Binding						Note on use in COVID-19 patients	Major Side Effects	Contraindications
			α1	β1	β2	DA	V1*	V2*			
									>0.03 units/min. Taper by 0.01 units/min every 30 - 60 min[97]		
Levosimendan[#]	Decompensated HF	Initial: 6 - 12 mcg/kg infused over 10 min. Maintenance: 0.05 - 0.2 mcg/kg/min				N/A			N/A	Tachycardia and hypotension[98]	None
Synthetic Angiotensin II[§]	Septic or other distributive shocks	Initial: 10 to 20 ng/kg/min (max dose of 80 ng/kg/min during the first 3 hours of treatment; max maintenance dose of 40 ng/kg/min); titrate every 5 minutes by up to 15 ng/kg/min. Down-titrate every 5 to 15 minutes by up to 15 ng/kg/min to wean[99]				N/A			Angiotensin II Receptor Blockers may diminish therapeutic effect. Angiotensin-Converting Enzyme Inhibitors may enhance therapeutic effects[99,100]	Use with concurrent VTE prophylaxis since arterial and venous thrombotic and thromboembolic events have been reported[99,100]	None

α_1, α-1 receptor; β_1, β-1 receptor; β_2, β-2 receptor; DA, dopamine receptors; + through +++++, minimal to maximal relative receptor affinity; N/A, not applicable; AHA; American Heart Association, ACCF; American College of Cardiology Foundation, HF; heart failure, CO; cardiac output, MAP; mean arterial pressure, CrCl; creatinine clearance, AV; atrioventricular, VTE; venous thromboembolism. PVCs; premature ventricular contractions

[*] V1 receptors (abundant in vascular smooth muscle), vasopressin stimulates GPCR, phosphatidylinositol/calcium pathway leading to vasoconstriction; V2 receptors (abundant in renal collecting duct system), vasopressin couples V2 receptors with the Gs signaling pathway, activating cAMP. Increased intracellular cAMP in the kidney triggers fusion of aquaporin-2-bearing vesicles with the plasma membrane of the collecting duct cells, thereby increasing water reabsorption.[101]

[#] Calcium sensitizer; exerts its positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C. Its vasodilatory effect occurs via opening adenosine triphosphate (ATP)-sensitive K^+ channels in vascular smooth muscle cells leading to vasodilation.[95] Drug not currently available in the US

[§] Acts via Ang II receptors causing (1) constriction of efferent arterioles in the kidneys and (2) in the adrenal glands causing the release of aldosterone.[95,99]

[**] Inotropic actions predominate at doses at the lower end of this range. Low dose: Renal dopamine receptors predominate. Intermediate dose: Dopamine and beta-adrenergic effects predominate. High dose: Alpha-adrenergic effects predominate.

[##] Except when (1) norepinephrine is associated with serious arrhythmias, (2) cardiac output is high and blood pressure persistently low, or (3) the combination of inotrope/vasopressor and low-dose vasopressin failed to achieve target MAP.[94]

[$] Should be combined with standard therapies. For renal dose adjustment, CrCl 10 to 50 mL/minute: Initial: 0.0625 to 0.125 mcg/kg/min and titrate cautiously. Titrating to >0.375 mcg/kg/min is not recommended

outweighed the risks, i.e., expected myocarditis cases after vaccination in the recommended populations.

CONCLUSIONS

Although known primarily for its effect on the pulmonary system, the SARS-CoV-2 virus is also notable for its extrapulmonary manifestations. Particularly, the cardiovascular system is prone to the direct and indirect effects of the virus whose affinity for tissues comprising this system remains wholly unclear, though mechanisms implicating the ACE2 receptor have been implicated. The cardiac complications of COVID-19 reported in the literature most notably include myopericarditis leading to shock and increased morbidity and mortality. Therefore, it is important that providers are made aware of these potential complications, anticipate treatment strategies, and familiarize themselves with tools at their disposal which can be utilized to improve overall outcomes

DECLARATION OF COMPETING INTEREST

None.

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