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WHITE PAPER

Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome

ABSTRACT: Coronavirus disease 2019 (COVID-19) is a rapidly expanding global pandemic caused by severe acute respiratory syndrome coronavirus 2, resulting in significant morbidity and mortality. A substantial minority of patients hospitalized develop an acute COVID-19 cardiovascular syndrome, which can manifest with a variety of clinical presentations but often presents as an acute cardiac injury with cardiomyopathy, ventricular arrhythmias, and hemodynamic instability in the absence of obstructive coronary artery disease. The cause of this injury is uncertain but is suspected to be related to myocarditis, microvascular injury, systemic cytokine-mediated injury, or stress-related cardiomyopathy. Although histologically unproven, severe acute respiratory syndrome coronavirus 2 has the potential to directly replicate within cardiomyocytes and pericytes, leading to viral myocarditis. Systemically elevated cytokines are also known to be cardiotoxic and have the potential to result in profound myocardial injury. Prior experience with severe acute respiratory syndrome coronavirus 1 has helped expedite the evaluation of several promising therapies, including antiviral agents, interleukin-6 inhibitors, and convalescent serum. Management of acute COVID-19 cardiovascular syndrome should involve a multidisciplinary team including intensive care specialists, infectious disease specialists, and cardiologists. Priorities for managing acute COVID-19 cardiovascular syndrome include balancing the goals of minimizing healthcare staff exposure for testing that will not change clinical management with early recognition of the syndrome at a time point at which intervention may be most effective. This article aims to review the best available data on acute COVID-19 cardiovascular syndrome epidemiology, pathogenesis, diagnosis, and treatment. From these data, we propose a surveillance, diagnostic, and management strategy that balances potential patient risks and healthcare staff exposure with improvement in meaningful clinical outcomes.

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Since the index cases were first reported in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic infecting >1 million individuals by early April 2020.[1,2] In addition to systemic and respiratory complications, COVID-19 can manifest with an acute cardiovascular syndrome (ACovCS; Table and Figure 1). In this document, we focus on a prominent myocarditis-like syndrome involving acute myocardial injury often associated with reduced left ventricular ejection fraction in the absence of obstructive coronary artery disease. This syndrome can be complicated by cardiac arrhythmias or clinical heart failure with or without associated hemodynamic instability, including shock.[1,3] These cardiac complications can occur precipitously at any point during hospitalization and are increasingly being described as a late complication that can occur after improvements in a patient's respiratory status.[4,5] ACovCS may be caused by acute coronary syndrome, demand ischemia, microvascular ischemic injury, injury related to cytokine dysregulation, or myocarditis.[6,7] This article aims to review the available data on ACovCS epidemiology, pathogenesis, diagnosis, and treatment. From these data, we propose a surveillance, diagnostic, and management strategy that balances patient and healthcare provider risks with potential improvement in meaningful clinical outcomes.

Table. Spectrum of ACovCS

Clinical Presentation	Key Manifestations
Acute coronary syndrome (STEMI or NSTEMI)*	Chest pain, elevated troponin, wall motion abnormalities, and/or ST-segment depression or elevation±T-wave abnormalities
Acute myocardial injury without obstructive CAD†	Elevated troponin±additional symptoms
Arrhythmias	Atrial arrhythmias, ventricular tachycardia, ventricular fibrillation, or complete heart block‡
Heart failure± cardiogenic shock	De novo systolic dysfunction
	Myocarditis or myopericarditis
	Cytokine-mediated cardiomyopathy
	Stress-induced cardiomyopathy
	Mediated through other risk factors (eg, atrial arrhythmias)
	Acute or chronic decompensated systolic dysfunction ±elevated troponin
	Recurrent systolic dysfunction after LVEF recovery
	Heart failure with preserved LVEF§
Pericardial effusion	±Tamponade
Thromboembolic complications	Arterial thromboembolism, deep vein thrombosis, intracardiac thrombus, microvascular thrombi,‡ pulmonary embolism, stroke

ACovCS indicates acute COVID-19 cardiovascular syndrome; CAD, coronary artery disease; COVID, coronavirus disease 2019; LVEF, left ventricular systolic dysfunction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Reported with obstructive, nonobstructive, or no coronary artery disease.

†It is uncertain whether an abnormal troponin is required before the onset of ACovCS. In addition, patients are reported to have either nonobstructive or no epicardial coronary artery disease.

‡Although these complications may be anticipated with our incomplete understanding of COVID-19, to the best of our knowledge, reports of heart block or cardiac microvascular thrombi have not been published to date.

§It is unknown at this time whether heart failure with preserved LVEF is part of this spectrum.

MYOCARDIAL INJURY IN PATIENTS WITH COVID-19

Acute myocardial damage during a viral illness may be inferred from rises in specific biomarkers, characteristic electrocardiographic changes, or new imaging features of impaired cardiac function. Prior experiences from Middle Eastern respiratory syndrome, severe acute respiratory syndrome (SARS), COVID-19, and non-SARS coronaviruses demonstrate that coronavirus can cause acute myocarditis.[7–12] In COVID-19, the frequency and differential patterns of troponin release in the context of a clinical presentation of a type 1 or 2 myocardial infarction, myocarditis, or cytokine/stress-related cardiomyopathy are not well defined. Anecdotal reports have described cases of acute myocardial injury characterized by marked cardiac troponin elevation accompanied by ST-segment elevation or depression on ECG and angiography often without epicardial coronary artery disease or culprit lesions identified.[11,13] These early data suggest that the dominant cause of myocardial injury for this phenotype is myocardial injury in the absence of epicardial coronary artery thrombosis. In addition, myocarditis, systemic cytokine-mediated, stress-related cardiomyopathy, or microvascular thrombosis could produce an acute myocardial injury pattern (Figure 2).

Acute myocardial injury as assessed by troponin release alone appears to complicate a substantial minority of hospitalized patients with COVID-19, particularly patients who require intensive care. Analysis of a series of 52 critically ill patients in China with COVID-19 revealed myocardial injury (high-sensitivity cardiac troponin I [cTnI] >28 ng/L) in 29% of patients.[14] Analysis of a second Chinese single-center retrospective report of 416 patients hospitalized with COVID-19 observed that ≈20% (82 of 416) of patients had an acute myocardial injury (cTnI >0.04 μg/L) and patients with myocardial injury were older and had a higher burden of comorbid disease.[15] Myocardial injury was associated with a higher observed mortality that persisted after adjustment for baseline characteristics and medical comorbidities.[15] A report from another Chinese multicenter retrospective study comprising data from 191 patients hospitalized with COVID-19 observed myocardial injury (cTnI >28 ng/L) in 1 of 95 (1%) surviving patients compared with 32 of 54 (59%) patients who did not survive.[16] Last, results from a meta-analysis revealed

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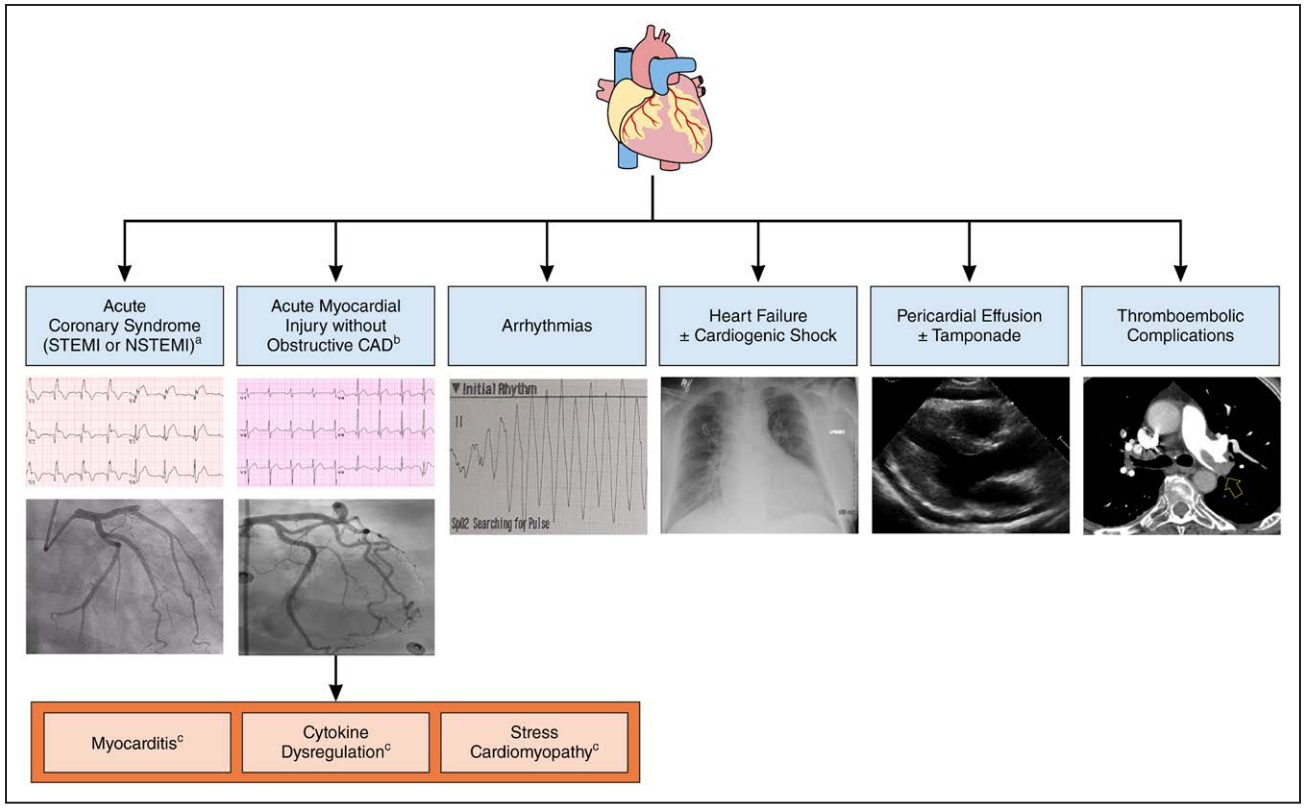

Figure 1. Spectrum of the acute coronavirus disease 2019 (COVID-19) cardiovascular syndrome (ACovCS).
The spectrum of ACovCS encompasses a variety of cardiovascular syndromes described for patients presenting with COVID-19. Reports of pericardial effusions and cardiac tamponade in patients with COVID-19 have been published. Although the prevalence of pericardial effusion in ACovCS remains uncertain, significant effusions do not appear to be common. Clinical images are representative of the proposed ACovCS disease spectrum, and several, but not all, images are from patients with ACovCS. [a]Reported with obstructive, nonobstructive, or no coronary artery disease (CAD). [b]It is uncertain whether an abnormal troponin is required before the onset of ACovCS, and patients are reported to have either nonobstructive or no epicardial CAD. [c]Significant uncertainty remains about the cause and prevalence of the acute myocardial injury for patients without obstructive CAD and COVID-19. Although myocarditis, cytokine storm, and stress cardiomyopathy are leading considerations, additional potential causes include hypoxemia and microvascular dysfunction from small vessel thrombosis. NSTEMI indicates non–ST-elevation myocardial infarction; and STEMI, ST-elevation myocardial infarction.

abnormal cTnI values (>99th percentile) in 8% to 12% of hospitalized patients with COVID-19, and elevations were associated with more severe complications and worse outcomes.[17] The mean difference in cTnI value was 25.6 ng/L (95% CI, 6.8–44.5) between those with (n=123) and those without (n=218) severe disease.[17] Although the troponin samples were not systematically collected and their ascertainment may be influenced by indication bias, these data support that acute myocardial injury is commonly observed in COVID-19 and is prognostic for worse outcomes.

The mechanism of acute myocardial injury in COVID-19 is unresolved. Several cases of clinically diagnosed myocarditis relating to COVID-19 (without histology or pathology but with supporting imaging) have been reported, including 1 case requiring venoarterial extracorporeal membrane oxygenation.[11,18,19] The patient treated with extracorporeal membrane oxygenation was also treated with steroids, intravenous immunoglobulins, and antiviral therapy and subsequently recovered.[19] In a case series of 150 patients, 5 of 68 (7%) patients who died were reported to have acute myocardial injury with heart failure, and another 22 of 68 (32%) were reported to have acute myocardial injury with heart failure as a contributing factor.[20] Limited autopsy and endomyocardial biopsy results have been reported, but a case report from Italy has described biopsy-proven acute lymphocytic myocarditis in an individual with COVID-19.[7] A second case report described a patient with COVID-19 presenting with acute myocardial injury and cardiogenic shock.[12] The patient underwent an endomyocardial biopsy that demonstrated low-grade myocardial inflammation and the absence of myocyte necrosis with localization of SARS-CoV-2 within macrophages but not cardiomyocytes.[12] This case confirms that SARS-CoV-2 can reside within the heart but does not provide evidence for cardiotropic viral cell entry. Together, these studies confirm that acute myocarditis is a mechanism of myocardial injury in some patients with COVID-19, although the proportion of myocardial injury related to acute lymphocytic myocarditis remains uncertain.

Additional reports from Wuhan indicate a significant proportion of nonsurviving patients also had elevated transaminases, lactate dehydrogenase, creatine kinase,

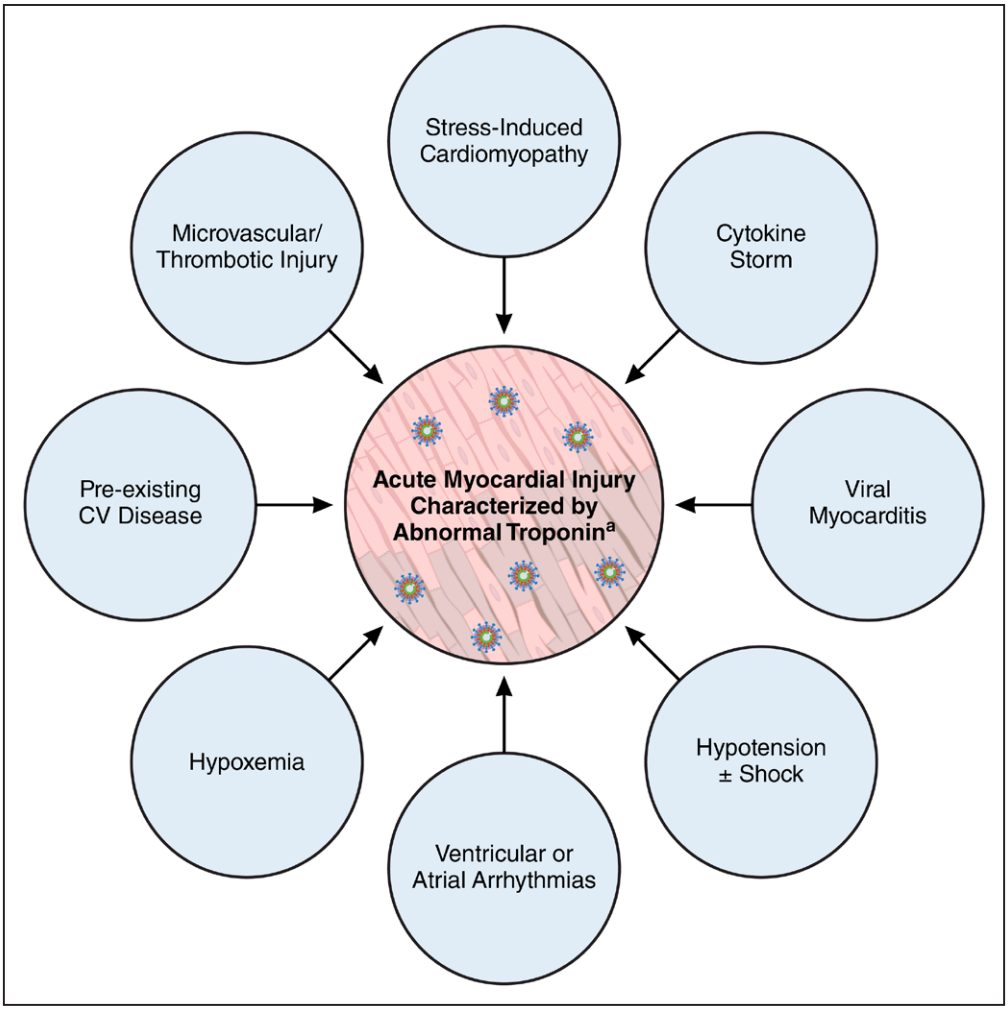

Figure 2. Potential mechanisms of myocardial injury in acute coronavirus disease 2019 (COVID-19) cardiovascular syndrome.
Multiple mechanisms have the potential to result in nonischemic myocardial injury in COVID-19. [a]Myocardial injury defined as cardiac troponin value >99th percentile of the upper reference limit.

D-dimer, serum ferritin, interleukin-6, and prothrombin time, which in totality suggest markedly elevated proinflammatory mediators and a cytokine profile similar to the cytokine release syndrome.[15,16] This constellation of inflammatory cytokines has inherent similarities to chimeric antigen receptor T–induced cytokine release syndrome, which results in marked elevations of interleukin-6 and interferon-γ.[21] For ACovCS, it is unclear to what extent such cytokine elevations cause or contribute to myocardial injury, left ventricular dysfunction, and cardiac troponin elevation. Additional studies, including collection of endomyocardial tissue by biopsy and autopsy studies, are required to delineate the pattern and proportion of ACovCS related to acute myocarditis versus general myocardial injury caused by systemic cytokine dysregulation.

COVID-19 TARGET TISSUES

The majority of prior experience with myocardial injury associated with viral infections is gleaned from data deriving from infections not related to coronaviruses. For example, clinical syndromes with COVID-19 suggest a higher prevalence of myocardial injury compared with that observed with wild-type coxsackie virus infections. The outbreak of SARS coronavirus 1 (SARS-CoV-1) in 2003, the SARS pandemic, resulted in investigations that have the potential to inform our understanding of SARS-CoV-2. Investigation into SARS-CoV-1 revealed that the virus expresses numerous spike (S) proteins on the surface of the viral envelope that are vital to the transmission of infection (Figure 3).[22] These S proteins bind through the S1 subunit to angiotensin-converting enzyme 2 (ACE2) expressed on host cells, but merely binding to ACE2 is not sufficient for cell infection.[22] Viral cell entry requires the transmembrane serine protease 2 (TMPRSS2) expressed on host cells to perform critical protein priming that leads to conformational changes, viral cell entry, and cell infection.[22,23] Investigation into SARS-CoV-2 has confirmed the importance of the S1 protein binding to ACE2 on target cells and the expression of the TMPRSS2 protease for host cell infection.[24]

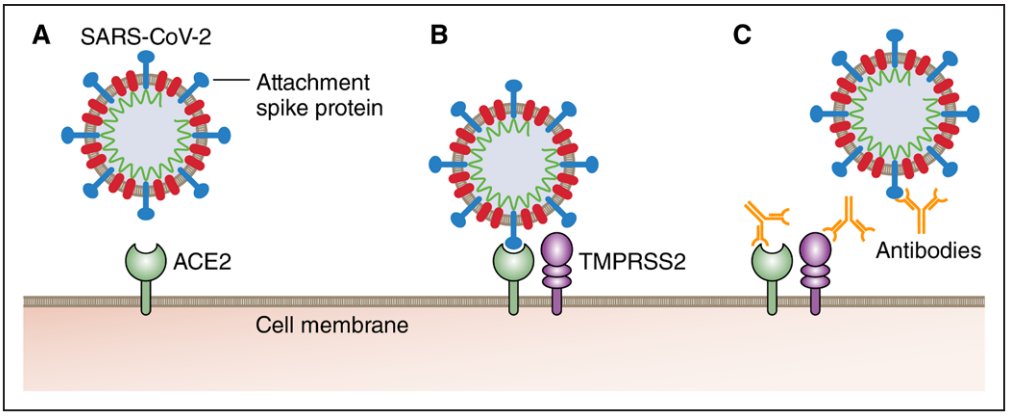

Figure 3. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) host cell entry.
A, Simplified mechanism of SARS-CoV-2 viral entry to host cells. The SARS-CoV-2 virus expresses spike proteins with an S1 subunit that binds to angiotensin-converting enzyme 2 (ACE2) expressed on host cells. **B**, After binding to host ACE2, the host transmembrane serine protease 2 (TMPRSS2) performs critical protein priming that leads to conformational changes, viral cell entry, and cell infection. **C**, Antibodies to the S1 subunit of the spike protein, ACE2, and TMPRSS2 are potential therapeutic targets that reduce viral infectivity.

Mechanisms that disrupt the S1 subunit binding, ACE2 binding, or TMPRSS2 protease activity are potential therapeutic targets. This theory was tested with the evaluation of the effect of antibodies to the S protein obtained from the convalescent serum of patients with SARS-CoV-2. Antibody administration reduced viral cell entry in a concentration-dependent manner, demonstrating partial successful inhibition of viral entry in an in vitro cell line.[24] Furthermore, the administration of anti-ACE2 antibodies has been demonstrated to inhibit SARS-CoV-1 and SARS-CoV-2 viral replication in an in vitro cell preparation in a dose-dependent fashion, further supporting the importance of the receptor as necessary for cellular entry.[22,24] In addition, early preclinical studies using recombinant ACE2 administration report effectively neutralizing SARS-CoV-1 and SARS-CoV-2 in vitro.[25] Last, inhibitors of the serine protease TMPRSS2 were effective in reducing cellular entry for both SARS-CoV-1 and SARS-CoV-2 in an in vitro model.[24] These studies clarify the mechanism of viral cell entry and highlight 3 distinct potential therapeutic targets that are theorized to reduce cellular entry and pathogenesis. The results from these small in vitro studies suggest that anti-ACE2, TMPRSS2 inhibitors, and inhibitors of S1 protein subunits may reduce viral propagation in host cells, although further study is required.

Given the essential nature of ACE2 for viral infection, the distribution of ACE2 expression is informative to elucidate the likely infected tissues and hypothetical mechanisms of injury. ACE2 is found prominently in type 1 and II lung alveolar epithelium; pericytes; cardiomyocytes; enterocytes in the small intestine, including the duodenum, jejunum, and ileum; and arterial and venous endothelial cells.[26–28] Autopsy studies in patients who died of SARS-CoV-1 have confirmed the presence of virus within cells that prominently express ACE2, including bronchiolar and alveolar epithelial cells, renal tubular epithelial cells, mucosal and crypt epithelial cells of the gastrointestinal tract, and cardiomyocytes.[29] Analyses of histological samples of pulmonary tissue in patients with COVID-19 reveal a pattern of injury similar to that reported for SARS-CoV-1.[30] Although these data are extremely limited for COVID-19 at this juncture, they offer proof of concept of direct cellular injury in tissues with ACE2 expression. The myocardial cellular targets for SARS-CoV-2 may include pericytes, cardiomyocytes, fibroblasts, and immune cells such as resident macrophages.

MYOCARDIAL PATHOLOGY

Pathological examination may help clarify whether myocardial injury predominately occurs indirectly as a result of systemic cytokines or directly as a result of viral cardiomyocyte infection or some other mechanism. Acute cellular injury caused by SARS-CoV-2 cardiomyocyte, pericyte, or fibroblast infection through ACE2-mediated entry and subsequent viral replication is a theoretical but unproven process. Analyses of histological specimens have demonstrated direct cellular viral infection of the myocardium and cells within the conduction pathways of the heart with SARS-CoV-1.[29,31,32] Prior acute myocarditis experience with alternative viruses suggests that direct cellular injury is related to a combination of cardiotropic viral entry into myocytes and the subsequent innate immune response that can lead to focal or diffuse myocardial necrosis.[33] Within a few days of this direct cellular injury, edema and necrosis can lead to contractile dysfunction and clinical symptoms.[33] If true in COVID-19, this delayed injury could potentially manifest as an abrupt clinical decline after several days of stability. Cardiotropic viruses such as SARS-CoV-1 are typically cleared from the myocardium within 5 days; however, infrequently, the virus may persist in the myocardium for several weeks to months.[34] Presuming that

SARS-CoV-2 can directly infect the myocardium, any associated myocarditis will be manifest predominately in the acute or subacute stage. It is also uncertain whether SARS-CoV-1 or SARS-CoV-2 leads to the production of cardiac autoantibodies that develop as a result of molecular mimicry, as previously demonstrated between coxsackie B virus proteins and the S2 regions of cardiac myosin.[35] Whether viral persistence or inflammation from COVID-19 can cause a chronic dilated cardiomyopathy as occurs after coxsackie B virus myocarditis is also unknown.

Alternatively, myocardial injury in COVID-19 may also result from profound inflammatory activation and cytokine release.[16] Analysis of a small case series of minimally invasive autopsy in 3 patients who died of COVID-19 described the presence of SARS-CoV-2 within alveolar tissue.[36] SARS-CoV-2 was not isolated from cardiac tissue, but degenerative changes and necrosis suggested a secondary mechanism of injury.[36] These preliminary observations raise the possibility that SARS-CoV-2, unlike SARS-CoV-1 as described earlier, may not directly cause cellular injury. Indeed, acute myocardial injury in the setting of non–COVID-19 viral immune activation can result from immune-mediated injury caused by activated T and B cells, leading to an inflammatory cascade, cytokine production, and antibody production.[33,37] Further studies in stress-induced and non–COVID-19 virus–associated cardiomyopathy have associated increased levels of cytokines with myocardial injury.[38,39] As discussed, a profound inflammatory response with marked cytokine production commonly occurs in hospitalized patients with severe or critical COVID-19.[16] This marked inflammatory response can also lead to the development of disseminated intravascular coagulopathy in critically ill patients. In 183 consecutive Chinese patients admitted with COVID-19, coagulopathy was associated with higher mortality, and 15 of 21 (71%) of nonsurviving patients met the criteria for disseminated intravascular coagulopathy.[40] Localized pulmonary arteriolar thrombosis was described in SARS, and pulmonary emboli have been reported in COVID-19.[41] Therefore, microvascular thrombosis in coronary vessels resulting from disseminated intravascular coagulopathy is another potential but unproven mechanism that may contribute to myocardial injury.[42]

In short, SARS-CoV-2 has the potential to infect cardiomyocytes, pericytes, and fibroblasts via the ACE2 pathway, leading to direct myocardial injury, but that pathophysiological sequence remains unproven. A second hypothesis to explain COVID-19–related myocardial injury centers on cytokine excess or antibody-mediated mechanisms. Further investigation via autopsy and endomyocardial biopsy tissue is needed to clarify which of these is the predominate mechanism of injury in ACovCS.

HISTORICAL OUTCOMES

Patients with acute viral myocarditis commonly present after a viral syndrome with clinical heart failure, chest pain, abnormal ECGs that can mimic an acute coronary syndrome, or ventricular arrhythmias.[43,44] This constellation of findings is increasingly being described in patients infected with COVID-19, raising suspicion for acute virus-associated injury from a myocarditis-like presentation.[6] There is a paucity of published data on the cardiac complications of Middle Eastern respiratory syndrome and SARS. Patients with preexisting cardiovascular disease have increased mortality for both SARS and COVID-19; however, cardiac complications appear to be less prevalent in SARS compared with COVID-19.[16,45]

DIAGNOSIS

Historically, patients are typically diagnosed with acute myocarditis if they have <30 days of symptoms with an abnormal troponin and cardiac magnetic resonance imaging findings meeting the revised Lake Louise 2018 criteria.[46,47] In non–COVID-19 cases, endomyocardial biopsy has traditionally been recommended in fulminant presentations to exclude the rare presentation of eosinophilic, hypersensitive, and giant-cell myocarditis.[48] However, in the setting of COVID-19, such an approach may not be feasible because of the instability of the patient, procedural risk, and risk of healthcare staff exposure, especially if the biopsy results would not change clinical management. Patterns of delayed myocardial enhancement consistent with acute myocarditis have also been described in contrast-enhanced ECG-gated multidetector computed tomography in non–COVID-19 cases.[49,50] This may be a useful rapid, noninvasive diagnostic test to assess for myocardial injury in patients with COVID-19 who complete a computed tomography scan for noncardiac reasons and represents an opportunity for investigation.

Given the extremely contagious and morbid nature of COVID-19, the priorities related to managing and diagnostic options for a patient with ACovCS include reducing staff/patient exposures, a goal that can be facilitated by limiting testing and patient transfer for diagnostic procedures, especially those that do not directly influence patient management. Another consideration is to limit testing that requires terminal room cleaning required by patient transfer because that process can add significant delays to diagnostic testing for other patients. Such strategies may result in increased uncertainty about the diagnosis but are unlikely to increase adverse short-term outcomes in patients without fulminant presentations. For example, for patients noted to have acutely elevated

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troponin, if a type 1 myocardial infarction can be excluded on clinical grounds, then a biopsy is unlikely to change immediate clinical management whether the clinical syndrome is caused by myocarditis, cytokine-induced myocardial injury, or a type 2 myocardial infarction. Therefore, routine endomyocardial biopsy in patients with active COVID-19 with abnormal cardiac biomarkers, regardless of fulminant or nonfulminant presentation, is discouraged. This strategy is aligned with recent American College of Cardiology recommendations.[51] However, an exception to that approach could be a patient with COVID-19 with hemodynamic or electrophysiological instability who undergoes coronary angiography to exclude obstructive coronary artery disease. In that setting, the patient is already in the catheterization laboratory, so the incremental infectious risk is reduced because additional transport is not needed. Such opportunities may be useful to gain insights into the mechanism of the acute myocardial injury, including the possibility of giant-cell myocarditis, which presumably can still occur during the COVID-19 pandemic.

In accordance with these guiding principles, the majority of patients with an abnormal troponin in the setting of COVID-19 infection can be followed up with expectant management until recovery from the acute viral syndrome. Extrapolating from prior experiences, patients with COVID-19 and myocardial injury who are hemodynamically and electrophysiologically stable with mild to moderate elevations of troponin should not routinely undergo an echocardiogram, angiography, or cardiac imaging. These diagnostic studies likely can be avoided altogether or delayed until recovery from COVID-19 unless the patient clinically deteriorates and develops hemodynamic instability, shock, ventricular arrhythmias, or a severely elevated or rapidly rising troponin (Figure 4). However, if the treating clinician has the ability to perform point-of-care cardiac ultrasonography without increasing COVID-19 exposure, this would be reasonable because a low ejection fraction would identify higher-risk patients and support earlier initiation of guideline-directed medical therapy once the patient is stable. However, unnecessary or repeated imaging not vital to clinical decision-making should be avoided in accordance with the American Society of Echocardiography COVID-19 statement.[52] Patients discovered to have newly diagnosed depressed left ventricular systolic function (left ventricular ejection fraction) without elevated troponin are more likely to have preexisting cardiomyopathy than myocarditis. Although the lack of definitive diagnostic studies may temporarily increase diagnostic uncertainty, it reduces the risk of COVID-19 transmission to staff and in clinically stable patients seems less likely to compromise short-term (<60 day) patient outcomes.

HISTORICAL TREATMENTS FOR SARS

Similar to COVID-19, SARS presented with a spectrum of symptoms, and the majority of patients required only supportive care.[53] Several antiviral agents, including ribavirin, were used empirically in patients with severe respiratory compromise.[53] Ribavirin for SARS was eventually abandoned because of a lack of antiviral activity against SARS-CoV-1 and lack of efficacy in clinical trials.[54,55]

Like patients with COVID-19, patients with SARS developed progressive respiratory failure despite declining viral loads and rising antibody concentrations, a deterioration theorized to be an immune-mediated injury related to either antibodies or elevated cytokine levels.[53,56,57] Steroid protocols were developed ranging from hydrocortisone 2 mg/kg IV 4 times daily to methylprednisolone 500 mg IV daily for 5 days with various taper protocols.[53] Steroid treatment for SARS yielded inconsistent benefit, with some studies associating steroids with increased mortality and a higher rate of intensive care and others suggesting modest radiographic or oxygen improvements.[53] A postmortem series of patients detected high viral loads in patients up to 30 days after illness onset, possibly because corticosteroids prolonged the duration of viral replication.[58] Additional therapies, including tumor necrosis factor-α blockers and convalescent plasma with anti–SARS-CoV-1 antibodies, were proposed but not rigorously studied. Although a concern, acute myocardial injury, including myocarditis, appeared uncommon, and there was scant published guidance for the management of SARS-CoV-1 myocardial injury.

TREATMENT OF ACovCS

There are no comprehensive expert recommendations and only limited data from high-quality studies to inform our clinical decision-making for the pharmacotherapy of ACovCS. Because most small case series and studies of viral myocarditis in general involve fulminant and otherwise complicated presentations, significant publication bias exists in the literature. Published experiences with COVID-19–associated myocardial injury are even more limited, including retrospective small case series and individual case reports. Thus, the best practices for treating the acute myocardial injury in ACovCS currently need to be extrapolated from prior non–COVID-19 experiences and the available limited-quality COVID-19 data. In general, treatment of ACovCS should be completed with a multidisciplinary team that includes infectious disease consultation to help guide therapy selection. Several experimental therapies attempting to limit SARS-CoV-2 replication or the immune response have been proposed with multiple clinical trials currently underway. At present, there are no therapies with rigorous

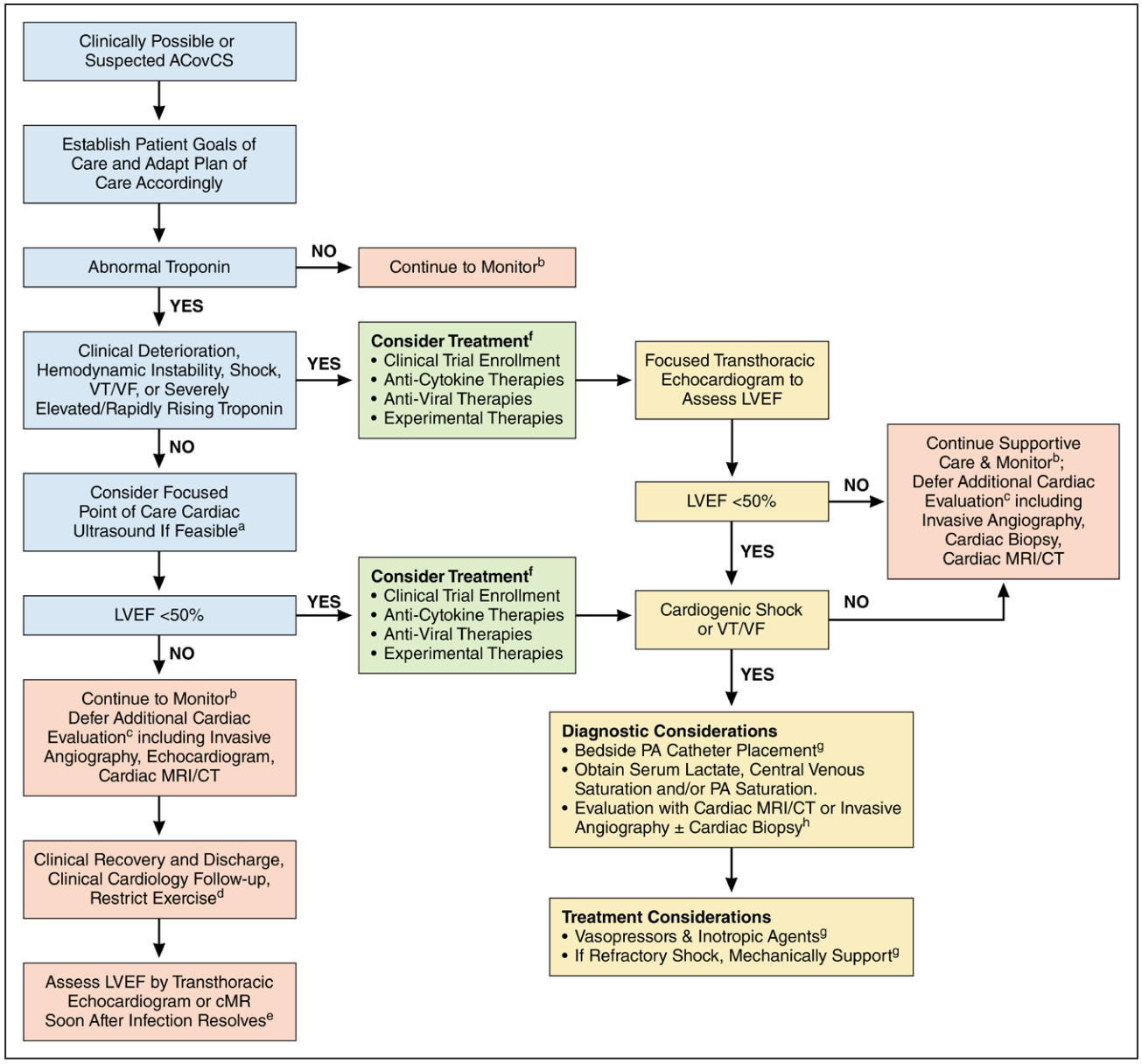

Figure 4. Proposed assessment and management of acute coronavirus disease 2019 (COVID-19) cardiovascular syndrome (ACovCS) with acute myocardial injury.

Proposed assessment and management of ACovCS with acute myocardial injury. [a]If the treating clinician has the ability to provide a point-of-care cardiac ultrasonography without increasing COVID-19 exposure or personal protective gear use, limited left ventricular ejection fraction (LVEF) assessment can be considered because a depressed systolic function would identify higher-risk patients. [b]Repeat troponin testing is indicated with a deterioration of clinical status. [c]This pathway attempts to balance the imperfect tradeoffs of increased diagnostic uncertainty without compromising patient outcomes while minimizing unnecessary staff exposures and testing that will not immediately change clinical care. [d]The 2015 Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities Task Force recommends abstinence from competitive sports or aerobic activity for a period of 3 to 6 months until resolution of myocardial inflammation. [e]Assessment of the LVEF should be considered at early follow-up for patients with an abnormal troponin during hospitalization either to identify patients with reduced systolic function or to complete a full cardiac assessment. Complete assessment should occur once a patient is no longer considered infectious in accordance with Centers for Disease Control and Prevention recommendations for the discontinuation of transmission-based precautions for patients with COVID-19. [f]There are currently no evidence-based therapies for COVID-19 with robust clinical evidence of efficacy. Enrollment in a clinical trial should be strongly considered if available at the treating center. Additional treatment with antiviral, anticytokine, and other investigational drugs should be completed on a case-by-case basis after consultation with a multidisciplinary team. [g]Pulmonary arterial catheters, inotropic, or mechanical support (ie, intra-aortic balloon pump, temporary left ventricular support device, veno-arterial extracorporeal membrane oxygenation) should be considered on a case-by-case basis, taking into account patient characteristics, availability of appropriately trained staff, and the ability of the healthcare institution to safely manage a support device. [h]Evidence of acute myocarditis by imaging or biopsy within myocardial tissue may modify the choice and dosing regimen of therapies. cMR indicates cardiac magnetic resonance; CT, computed tomography; MRI, magnetic resonance imaging; PA, pulmonary artery; and VT/VF, ventricular tachycardia/ventricular fibrillation.

clinically supported efficacy for COVID-19 in general or for ACovCS specifically. If possible, enrollment in ongoing clinical trials is encouraged.

Hydroxychloroquine is a proposed treatment for COVID-19 on the basis of in vitro testing and a small open-label study with significant methodological

limitations.[59] The clinical study enrolled 42 patients: 26 patients receiving hydroxychloroquine and 16 controls. Only 36 patients were included the analysis because 6 (23%) of the hydroxychloroquine-treated patients were lost to follow-up.[59] The study authors concluded that hydroxychloroquine had a significant effect and led to rapid SARS-CoV-2 clearance.[59] This conclusion appears overstated on the basis of the study design and results, and we believe that further studies of hydroxychloroquine, including its effect on ACovCS, are required.[60]

Antiviral therapies may have a role in the treatment of ACovCS. The use of lopinavir/ritonavir for severe COVID-19 was tested prospectively in 199 patients but unfortunately did not lead to a significant reduction in viral load or symptomatic improvement.[57] Remdesivir has also been proposed as an antiviral therapy after originally being developed for Ebola and the Marburg virus. Subsequent investigation demonstrated significant reduction of viral replication and symptoms in a mouse model infected with SARS-CoV-1.[61] Additional in vitro testing of a human cell line demonstrated markedly reduced SARS-CoV-2 activity.[62] This led to compassionate use of remdesivir in patients with COVID-19, an effort that was eventually suspended with the initiation of currently enrolling prospective clinical trials.[62] Both hydroxychloroquine and antiviral therapies may increase the risk for torsades de pointes through QTc prolongation.[63] This risk may be increased in ACovCS if there are abnormalities of cardiac structure or function (eg, left ventricular hypertrophy or reduced ejection fraction), concomitant ventricular arrhythmias, or a prolonged QT interval at baseline.

Immunosuppression for myocardial injury in ACovCS has been proposed as a treatment option; however, prior experiences with broad immunosuppression for acute myocarditis historically have not been favorable. In the Myocarditis Treatment Trial, no significant difference was seen in left ventricular ejection fraction or survival between patients treated with cyclosporine/prednisone, those treated with azathioprine/prednisone, and those receiving placebo among patients with myocarditis in the pre-COVID era.[64] Although there were several limitations of the trial, these results do not support widespread use of immunosuppressive therapies for myocarditis. A systematic Cochrane review evaluated the efficacy of steroids for acute viral myocarditis in 8 randomized controlled trials with a total of 719 patients in the pre-COVID era. Those investigators concluded that glucocorticoid therapy did not reduce the composite end point of mortality or heart transplantation.[65] Steroid use in severe COVID-19 appears common in reports, and use is numerically higher in nonsurvivors, although that observation is likely confounded by indication for steroid initiation.[16] Given the concern that steroids may prolong SARS-CoV-2 viral persistence, corticosteroid treatment should not be routine but rather may be considered salvage therapy with multidisciplinary input in select cases of hemodynamically unstable patients.[58]

As discussed, cytokine activation appears to be a prominent feature of severe COVID-19 illness and ACovCS with marked elevations of interleukin-6 and other inflammatory markers. Sarilumab, siltuximab, and tocilizumab are interleukin-6 inhibitors that have potential utility in ACovCS and severe COVID-19.[66] Tocilizumab is approved by the US Food and Drug Administration to manage cytokine release syndrome resulting from chimeric antigen receptor T cell therapy and is being investigated for pneumonitis induced by immune checkpoint inhibitors.[21,67] Trials with sarilumab, siltuximab, and tocilizumab are underway in patients with COVID-19 and will provide additional information on therapeutic efficacy and safety and the impact on ACovCS.[68–70] In the interim, these agents can be considered for compassionate use on a case-by-case basis with multidisciplinary input.

Given the known association between myocarditis and autoantibodies, intravenous immunoglobulin is theorized as a possible treatment for virus-associated myocarditis. However, in a well-conducted study in the pre-COVID era, intravenous immunoglobulin did not improve left ventricular ejection fraction or event-free survival at the 1-year follow-up.[71] This study highlighted the lack of high-quality evidence for the routine use of intravenous immunoglobulin to treat idiopathic dilated cardiomyopathy or myocarditis, although the treatment appeared safe. Use of 1 g/kg IV immunoglobulin daily for 2 days can be considered in select cases of hemodynamically unstable patients with suspected fulminant myocarditis as salvage therapy with multidisciplinary input. However, it is important to note that this is an extremely limited resource and should be reserved for patients with high clinical suspicion of cardiomyopathy resulting from myocarditis rather than cytokine storm or stress-induced cardiomyopathy.

More focused antibody therapy using convalescent plasma from recovered patients with COVID-19 has been approved recently by the US Food and Drug Administration.[72] A recent report described treatment of 5 critically ill patients with convalescent plasma containing a SARS-CoV-2–specific antibody (immunoglobulin G) obtained from survivors of COVID-19.[73] In this uncontrolled case series, investigators reported an improved clinical status, an observation that merits further clinical investigation.

If myocardial injury is diagnosed clinically and the patient recovers from COVID-19, similar to historical expert opinion recommendations for non-COVID myocarditis, abstinence from competitive sports or aerobic activity would be reasonable for a period of 3 to 6 months until resolution of myocardial inflammation by cardiac magnetic resonance imaging or normalization of troponin.[74]

This recommendation is based on experimental animal models and several retrospective observational studies.[74–76] The initiation of guideline-directed medical therapy may be considered for all patients with suspected myocarditis and reduced systolic function in accordance with the most recent guidelines for the management of heart failure after a period of clinical stability and improvement such that individuals are preparing for discharge.[77] We advise delaying guideline-directed medical therapy until that later time point given that respiratory status can deteriorate rapidly earlier in the illness and require intubation, leading to hypotension.

Last, in select cases with refractory shock or ventricular arrhythmias caused by ACovCS, mechanical support can be considered if available at the treating facility. Case reports have described successful rescue of patients with cardiogenic shock with the use of veno-arterial and veno-arterial-veno extracorporeal membrane oxygenation.[5,12,19] If cardiogenic shock is suspected secondary to myocarditis, expert consultation with an advanced heart failure team should be strongly considered.

SUMMARY

COVID-19 is associated with the development of a cardiovascular syndrome including acute myocardial injury, arrhythmias, and cardiomyopathy that we have called ACovCS. It is uncertain to what extent the acute systolic heart failure is mediated by myocarditis, cytokine storm, microvascular dysfunction, small vessel thrombotic complications, or a variant of stress-induced cardiomyopathy. Patients with elevated troponin who are otherwise clinically stable do not require extensive cardiac imaging during the acute phase of COVID-19 if point-of-care cardiac ultrasound is not available. Patients with hemodynamic instability or ventricular arrhythmias require more detailed evaluation, cardiology consultation, and consideration for enrollment in clinical trials or experimental therapies.

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