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SARS-CoV-2 and myocardial injury: Few answers, many questions

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■ **ABSTRACT**

Patients with COVID-19 and acute cardiac injury as measured by an elevated high-sensitivity troponin I or troponin T upon admission or during hospitalization have a mortality rate of over 50% in initial reports. The mechanism of SARS-CoV-2 and associated myocardial injury, whether SARS-CoV-2 patients with myocardial injury are a distinct population, and possible treatment options for myocardial injury associated with SARS-CoV-2 are unknown.

■ **MYOCARDIAL INJURY AND COVID-19**

Initial case-fatality rates from SARS-CoV-2, the coronavirus causing coronavirus infection 2019 (COVID-19), have ranged from 2.3% to 7.3%,[1,2] and given the burden of disease, the devastation is singularly alarming and unprecedented. Even though the predominant manifestations are respiratory, concomitant cardiovascular complications result in substantial morbidity and mortality.[3] Similar to prior investigations with viral infections, acute cardiac injury in COVID-19 has been defined primarily as an elevation in serum cardiac markers above the 99th percentile upper reference range, and the incidence has ranged from approximately 8% to 28%.[4–7] Using the broad and inclusive definition of acute cardiac injury as an elevated high-sensitivity troponin I or troponin T upon admission or during hospitalization, the mortality rate has been striking—over 50% in initial reports.[5,6] Given this startling signal, amid our ever-changing understanding of this pandemic, the following questions warrant emphasis:

1. What is the mechanism of SARS-CoV-2 associated myocardial injury?
2. To what extent are SARS-CoV-2 patients with myocardial injury a distinct population?
3. What are possible treatment options for myocardial injury associated with SARS-CoV-2?

With regards to mechanism, the primary question is whether SARS-CoV-2 precipitates myocardial infarction with an oxygen supply-demand imbalance, either with or without acute coronary plaque pathology (type I and II myocardial infarction) or conversely, causes myocardial injury mediated by viruses or cytokines. Viral infections are well known to lead to adverse cardiovascular events either by increased metabolic demand in the setting of limited cardiac reserve, or by precipitating plaque rupture in the setting of inflammation and a prothrombotic state.[8] Of note, influenza vaccination has been shown to reduce hospitalization for cardiac disease.[9] In addition, certain viruses (eg, parvovirus-B19 and influenza) commonly cause myocarditis. However, myocardial infarction and injury have not been prominent with other coronaviruses, and unfortunately, SARS-CoV-2 appears to be behaving differently.

Despite an overall case-fatality rate of approximately 10% in symptomatic patients, cardiac complications from the previous SARS-CoV outbreak that resulted in severe acute respiratory syndrome (SARS) are anecdotal and limited to cases reports or series.[10] Similarly, despite an even higher case-fatality rate, cardiac complications in the setting of Middle East respiratory syndrome coronavirus (MERS-CoV) are limited.[8,11] By contrast, in an initial report of causes of death in COVID-19, one-third were considered secondary to respiratory failure with myocardial damage, and nearly another tenth were considered secondary to myocardial damage alone.[12] Furthermore, perimyocarditis from SARS-CoV-2 has been reported in the absence of symptomatic respiratory disease,[13] though

fulminant myocarditis—generally defined as sudden and severe inflammation of the myocardium resulting in myocyte necrosis, edema, and cardiogenic shock—seems to be a rare presentation with SARS-CoV-2.

Of note, SARS-CoV-2 enters respiratory and cardiac cells via angiotensin-converting enzyme 2 (ACE 2), a membrane-bound protein.[3,8] Yet this potential cardiac tropism offers an incomplete explanation for the seemingly disproportionate cardiac manifestations of COVID-19, given that SARS-CoV also uses ACE 2 as a functional receptor.[14,15] Alternatively, myocardial injury may be exacerbated by an inappropriate activation of type I T-helper cells and cell-mediated immunity with associated cytokine storm.[3]

These putative mechanisms of injury are integrally entwined with the second question of whether patients with SARS-CoV-2–associated myocardial injury represent a distinct population. For one, COVID-19 patients with elevated troponins are older and have more cardiovascular comorbidities, such as coronary artery disease, chronic heart failure, hypertension, and diabetes mellitus.[5,6] These findings support myocardial oxygen supply-demand mismatch with resultant ischemia in a vulnerable population.

However, in patients who succumb to COVID-19, the troponin may continue to rise throughout the illness, a pattern distinct from the typical rise and fall after an ischemic insult.[6] Moreover, in some patients, this troponin elevation goes beyond what is typically observed in type II myocardial infarction.[16] Importantly, patients with elevated troponins have higher levels of C-reactive protein (CRP). The increases in troponin and CRP appear to parallel each other, and the overall correlation is similar in magnitude to the correlation between troponin and N-terminal pro-brain natriuretic peptides. These observations, though nascent, suggest that some patients may develop a hyperinflammatory state that perpetuates the nonischemic myocardial injury. Given that an elevated troponin is associated with a high mortality rate and that the mechanism of injury could be related to hyperinflammation, as more data are emerging, consideration should be given to checking troponin upon admission, with surveillance testing during the initial days of hospitalization.

Further considerations in this initial clinical approach include assessing whether the presentation is characterized by a modest troponin elevation in a patient with cardiac risk factors or a more substantial troponin elevation in a patient with hyper-

inflammation. With regards to the former, a rise and fall of cardiac markers and the presence of signs and symptoms of myocardial ischemia, such as new ischemic changes on electrocardiography or imaging evidence of regional myocardial dysfunction in a pattern compatible with ischemia, diagnoses a type II myocardial infarction. The absence of these features defines myocardial injury, and more substantial elevations in troponin and levels of CRP may favor hyperinflammatory myocardial injury. Traditionally, cardiac imaging would feature prominently in the distinction between acute myocardial infarction and injury. Given limited resources and the need to minimize exposure to COVID-19 patients, this decision will be individualized, though it will most likely involve selective use of focused echocardiography.

Of note, the overlap between acute myocardial infarction and noninflamed and hyperinflamed myocardial injury remains to be defined, though it may be considerable, and identifies a patient at the highest risk. An elderly patient with coronary artery disease, diabetes mellitus, and marked elevations in troponin and CRP will have among the poorest prognosis. Still, in evaluating patients with an elevated troponin, we are well accustomed to risk stratification according to cardiovascular comorbidities, but with COVID-19, we should also risk-stratify based on the degree of hyperinflammation.

Finally, the consideration of treatment options in a patient with a positive troponin is informed by the presumed answers to the first two questions. Specifically, does the mechanism of injury seem more likely related to myocardial infarction with oxygen supply-demand mismatch or direct myocardial injury? And is this a patient with underlying cardiac conditions, hyperinflammation, or both? Treatment strategies for type I myocardial infarction are well delineated, and treatment of type II myocardial infarction includes addressing the underlying cause and providing therapies to improve the myocardial oxygen supply-demand mismatch, especially in the setting of known fixed coronary stenosis. Importantly, therapies such as beta-blockers and vasodilators must be used judiciously to avoid precipitation of decompensated heart failure or shock. In this setting, revascularization is rarely indicated, and the benefit of antiplatelet and anticoagulant therapy is unknown.

With COVID-19, treatment is supportive and may include antivirals. However, in severe disease, morbidity and mortality may be driven by hyperinflammation.[17] Hyperinflammation may progress to secondary hemophagocytic lymphohistiocystosis

and resultant fatal hypercytokinemia with multiorgan failure. In this inflammatory state, immunosuppression may improve outcomes.

In particular, promising immune treatments for cardiac disease target autoinflammation, a process driven by endogenous danger signals and perpetuated by inflammasome-induced cytokine production. Such therapies have demonstrated efficacy in cardiac disease, including colchicine and anakinra in pericarditis and colchicine and canakinumab in atherosclerotic disease.[18–21] Colchicine inhibits tubulin polymerization and inflammasome activity, whereas anakinra and canakinumab inhibit interleukin-1, a cytokine that is central to the interleukin-6 signaling pathway, a target that has shown promise in treating severe COVID-19 pneumonia. Accordingly, anakinra is being studied in acute myocarditis (NCT03018834), and in COVID-19, trials are now under way with colchicine (NCT04326790, NCT04322565, NCT04322682) and anakinra (NCT04324021).

In conclusion, for troponin-positive COVID-19 patients, we currently have few answers and many questions. Given the resolve and collaboration of the medical community, we will certainly soon have an exhaustive list of the causes of acute cardiac injury. In general, for the clinician, we can consider three broad categories: (1) the patient with ischemic ST elevation, who needs emergency reperfusion therapy; (2) the patient with lower levels of troponin elevation in the setting of myocardial oxygen supply-demand mismatch, who needs supportive care; and (3) the patient with a greater degree of troponin elevation and hyperinflammation, who may need immunosuppressive therapy (**Figure 1**). As yet, the incidence and overlap in each of these categories are unknown, but in the patients in category 3, we may soon have effective therapies that target the inflammasome.

Figure 1. Three broad causes of acute cardiac injury.

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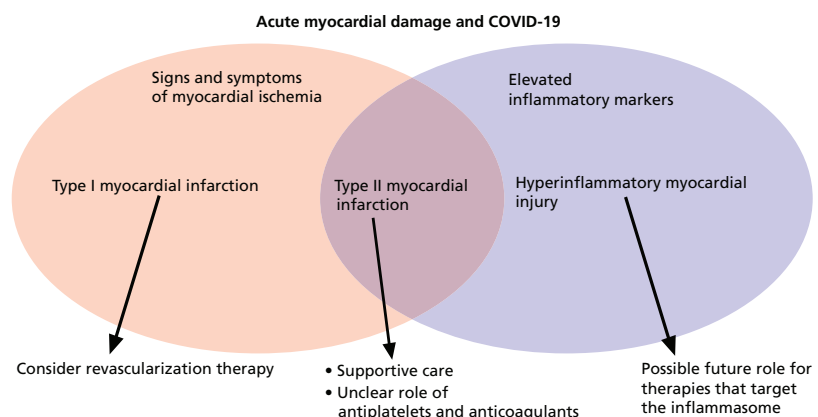3. **Zheng YY, Ma YT, Zhang JY, Xie X.** COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020; Mar 5. doi:10.1038/s41569-020-0360-5

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