

COVID-19 and acute myocardial injury: the heart of the matter or an innocent bystander?

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In the span of a few months, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has permeated the mindset and overshadowed priorities throughout the world. Within public health and clinical hospital systems, the persistent and surging threat of the coronavirus disease 2019 (COVID-19) pandemic dictates patient care. Concurrently, the focus of many researchers has transformed into a race against the pandemic to mitigate the spread of disease, and to recognise high-risk cohorts and characterise underlying mechanistic pathways of disease progression in efforts to discover effective treatments.

In the current study by Wei and colleagues,¹ the authors evaluated a consecutive cohort of 101 patients with COVID-19, admitted between 10 January and 10 March 2020 in Sichuan, China. They found that 15.8% of the hospitalised COVID-19 cohort demonstrated elevations in high-sensitivity troponin T, which was correlated with an increased risk for adverse outcomes including mortality. This study provides a snapshot of myocardial injury in cases of COVID-19 from a region not as overwhelmed by the pandemic as Wuhan, China. With less competition for scarce resources, thresholds for hospital admission, testing and level of care likely differed considerably between the two provinces.

There is substantial variation in case fatality rates between countries, ranging from 0.3% in Germany to 8.6% in Italy.² Although data across countries are lacking for cardiac biomarkers, rates of myocardial injury in patients with COVID-19 will likely exhibit similar variation between countries as well. To date, the majority of existing data on myocardial injury are from Wuhan—but even within the same region, reported

rates of myocardial injury have varied from 7.2% to 27.8%^{3–7} (table 1).

Several explanations for this variability exist. The foremost lies within case ascertainment driven by testing availability. The true denominator of individuals with COVID-19 remains unknown as a fraction of cases are either asymptomatic or mildly symptomatic, leading to undertesting and under-reporting, and subsequently biasing estimates of prevalent disease, risk factors and incident cardiovascular events. Additionally, there is considerable heterogeneity in defining myocardial injury across studies. Variability also exists within demographics (including age, lifestyle and socioeconomic factors) and clinical comorbidities from region to region and across countries, leading to tangible differences in risk. Thus, we need consistent testing of populations for COVID-19, systematic data collection and biomarker testing, standardised definitions and consistent reporting from countries to more accurately estimate rates of myocardial injury and its associated clinical implications.

POTENTIAL MECHANISMS OF MYOCARDIAL INJURY

Across studies to date in patients with COVID-19, elevated troponin has consistently been associated with worse outcomes. What remains unknown is the mechanism of myocardial injury as we are limited in the degree of myocardial characterisation in most cases. It is highly probable that there are a number of different aetiologies^{2,8} that may vary by individual case and overlap in many instances. Putative mechanisms include:

1. Myocardial injury may be due to unmasking of underlying cardiovascular disease. The prevalence of baseline cardiovascular comorbidities is high with COVID-19 (table 1), particularly in those with more severe disease. If there is pre-existing cardiovascular disease, the lack of cardiac reserve would predispose to injury in setting of a physiological stress response.
2. Acute coronary syndrome (ACS) either due to plaque rupture, demand ischaemia or vasospasm is certainly

conceivable. Given haemodynamic changes and exaggerated inflammatory response frequently seen with COVID-19, risk for ACS is heightened.⁸

3. Cytokine release syndrome (CRS) has been suspected in cases where increasing troponin I tracks with other inflammatory biomarkers (including D-dimer, interleukin-6 (IL-6), interferon-alpha, ferritin and C-reactive protein).² These cases are reminiscent of what we have observed in cardio-oncology with chimeric antigen receptor T-cell therapy and cytokine storm. As IL-6 is a key mediator of CRS, treatment is typically with IL-6 antagonists, with steroids as second-line therapy.
4. Studies from historical epidemics with other coronavirus species have demonstrated cases of myocarditis based on cardiac MRI. Mononuclear infiltrates in myocardial tissue consistent with myocarditis have been described in postmortem case reports of COVID-19.⁸ Although myocarditis has been suspected in many cases of COVID-19, definitive confirmation requires tissue histology and immunohistochemistry and has not been frequently pursued; hence, the true frequency of myocarditis remains unknown. Consensus statements in heart failure (HF) recommend endomyocardial biopsy for cases of fulminant HF, unexplained new-onset HF that fails to respond to usual care or when a specific diagnosis would alter management; suspected myocarditis in COVID-19 may meet these criteria. However, immunosuppression for lymphocytic myocarditis has not shown consistent benefit and whether this applies to COVID-19 is unknown.
5. Stress cardiomyopathy is frequently precipitated by acute emotional or physical stress, and can be triggered by increased sympathetic stimulation, high catecholamine states, microcirculatory dysfunction, vasospasm and proinflammatory states, all of which can occur with COVID-19. It remains a diagnosis based on identification of an acute trigger and exclusion of other cardiovascular disease. A clue may be in the biomarker profile, in which case peak troponin is disproportionately low relative to the degree of cardiac dysfunction, while B-type natriuretic peptide levels are markedly elevated.

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Table 1 Selected studies with description of myocardial injury in COVID-19

Study	Location	n for total cohort	Age (years)	Pre-existing cardiac disease	Definition of myocardial injury used in study	Per cent with myocardial injury
Wang <i>et al</i> ⁶	Wuhan, China	138	Median 56.0 (IQR 42.0–68.0)	15% cardiovascular disease 31% hypertension	Cardiac injury=troponin I above 99th percentile upper reference limit or new abnormalities on electrocardiography or echocardiography	7.2
Huang <i>et al</i> ⁴	Wuhan, China	41	Median 49.0 (IQR 41.0–58.0)	15% cardiovascular disease 15% hypertension	Cardiac injury=troponin I above 99th percentile upper reference limit or new abnormalities on electrocardiography or echocardiography	12
Wei <i>et al</i> (current study) ¹	Sichuan, China	101	Median 49.0 (IQR 34.0–62.0)	5% coronary artery disease 21% hypertension	Myocardial injury=high-sensitivity troponin T greater than institutional upper limit of normal	15.8
Zhou <i>et al</i> ⁷	Wuhan, China	191	Median 56.0 (IQR 46.0–67.0)	8% coronary heart disease 30% hypertension	Cardiac injury=high-sensitivity troponin I above 99th percentile upper reference limit or new abnormalities on electrocardiography or echocardiography	17
Shi <i>et al</i> ⁵	Wuhan, China	416	Median 64.0 (range 21.0–95.0)	4% chronic heart failure 11% coronary heart disease 31% hypertension	Cardiac injury=troponin I above 99th percentile upper reference limit, regardless of new abnormalities on electrocardiography or echocardiography	19.7
Guo <i>et al</i> ³	Wuhan, China	187	Mean 58.5±14.7	4% cardiomyopathy 11% coronary heart disease 33% hypertension	Myocardial injury=troponin T above 99th percentile upper reference limit	27.8

EMERGING THERAPIES

Although studies have shown myocardial injury to be a poor global prognosticator in COVID-19, we do not know whether attenuating myocardial injury would alter the final endpoint of death. Moreover, it remains unclear whether myocardial injury serves as the intermediary between COVID-19, systemic disease and mortality, or whether myocardial injury is a marker of systemic organ failure and a by-product of advanced disease.

A look into ClinicalTrials.gov finds many ongoing and upcoming trials of investigational agents for COVID-19. These range from the widely discussed hydroxychloroquine to block SARS-CoV-2 cell entry, antivirals including remdesivir, combination protease inhibitor lopinavir/ritonavir, recombinant ACE2 that may protect against lung injury, IL-6 receptor antagonists, vascular endothelial growth factor inhibitors, interferon, steroids and a number of other agents.^{2 8} However, the balance of risk-to-benefit is impacted by efficacy and appropriateness of treatment. For example, immunomodulatory

treatments may not be the best option when the mechanism of myocardial injury is stress cardiomyopathy or ACS, unless there is a non-cardiac indication for administration.

Due to the large number of experimental and emerging therapies, it is important to take a step back and clarify the mechanism of myocardial injury in individual cases when possible. There is heterogeneity between patients and a one-size-fits-all strategy may not be pragmatic once COVID-19 progresses to organ dysfunction inclusive of the cardiovascular system. Even if mechanisms of myocardial injury overlap, the ability to identify the trigger at a given time point may be more encouraging of a specific targeted therapy.

CHARACTERISING MYOCARDIAL INJURY FROM COVID-19

What can be done to gain a better understanding of myocardial injury? Endomyocardial biopsy can be diagnostic when there is concern for myocarditis. However, this is often restricted by the need to reduce additional exposure and

in the setting of non-myocarditis causes of myocardial injury, the diagnostic utility may be low. Given these concerns, advanced imaging with cardiac MRI would be the preferred non-invasive modality for tissue characterisation and can serve as a surrogate for biopsy to differentiate between aetiologies of myocardial injury. Nonetheless, challenges with exposure during patient transport and contamination of the MRI scanner limit widespread adoption.

To date, most centres have not performed comprehensive echocardiograms in cases of myocardial injury for similar concerns regarding risk to healthcare providers and contamination of equipment. To address this constraint, there has been growing interest and several initiatives to use point-of-care ultrasound (POCUS) for characterising systolic function and strain. The ability to rapidly identify regional wall motion abnormalities provides discriminatory ability to differentiate between the causes of myocardial injury, although it is unlikely to be confirmatory. For example, stress cardiomyopathy may

Table 2 Potential mechanisms of myocardial injury and diagnostic limitations due to COVID-19

Potential mechanism of myocardial injury	Standard method of diagnosis	Limitations to diagnostic modalities in setting of COVID-19 pandemic
Acute coronary syndrome	Trajectory of troponin and ECG changes; coronary angiography	Risk for healthcare worker exposure; higher threshold before taking patients to cardiac catheterisation lab in setting of myocardial injury
Cytokine release syndrome-induced myocardial dysfunction	Inflammatory and cardiac biomarker testing (often need to exclude coexisting cardiac diagnoses)	Minimal exposure with biomarker testing if timed with other blood draws; but limited by risk for exposure when excluding underlying cardiovascular disease
Myocarditis	Cardiac MRI for tissue characterisation (Lake Louise criteria); trajectory of cardiac biomarkers; endomyocardial biopsy in selected cases	Risk for exposure during transport and contamination of MRI scanner; risk for healthcare worker exposure in cases requiring biopsy
Progression of existing cardiovascular disease or demand ischaemia	Review of prior medical records and clinical history; cardiovascular disease-specific testing	Limited by risk for exposure if assessing for underlying cardiovascular disease
Stress-induced cardiomyopathy	Accurate clinical history taking for physical and psychological stressors; cardiac imaging patterns of wall motion abnormality that typically do not fit within a coronary distribution; diagnosis of exclusion (typically after excluding coronary artery disease)	None directly, but limited by risk for exposure when excluding underlying cardiovascular disease

mimic ACS or focal myocarditis on echocardiography.

There may be a heightened role for systematic biomarker surveillance in COVID-19 given the aforementioned limitations to standard diagnostic imaging and cardiac testing (table 2). Standardised cardiac and inflammatory biomarker testing in combination with POCUS and clinical correlation may provide more accurate phenotyping in many cases while constraining exposure. For example, if CRS is felt to be the leading culprit, then we would anticipate an uptrend in both cardiac and inflammatory biomarkers without regionality in left ventricular dysfunction. Correlation with postmortem pathological examination may confirm accuracy of diagnosis, although autopsies have also been limited by similar concerns of exposure to healthcare workers.

Currently, treatment of acute myocardial injury in patients with COVID-19 is analogous to driving into unknown territory without navigation—patient care is driven by what we perceive as the correct path. Despite our best efforts, there will be cases where we make the wrong clinical decision. A better understanding of the drivers of myocardial injury on a case-by-case basis would provide guidance in decision-making and steer clinicians towards the right direction of

treatment to maximise the chance of myocardial recovery.

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