Circulation

ON MY MIND

High-Sensitivity Cardiac Troponin Can Be an Ally in the Fight Against COVID-19

Andrew R. Chapman, MD, PhD
Anda Bularga, MD
Nicholas L. Mills, MD, PhD

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel pathogen responsible for the now widely recognized coronavirus disease 2019 (COVID-19). There are no evidence-based treatments for COVID-19, and the mainstay of management is supportive care. Mortality estimates for the condition vary, with a reported overall case-fatality rate between 1.4% and 2.3%.[1,2] Although a minority of patients have severe illness, the observed exponential spread of COVID-19 across many countries indicates that the critical care capacity in every region and country may become overwhelmed. It is imperative that we risk-stratify patients to determine those at highest risk who may require more intensive surveillance and support. Similarly, in patients most vulnerable to adverse outcomes, early recognition of a clinical state that is incompatible with survival may inform clinical decision making to prioritize palliative care and influence resource allocation, in a manner similar to triage after a major incident.

The American College of Cardiology recently published a short review of the role of biomarker testing in patients with COVID-19. It states that "clinicians are advised to only measure troponin if the diagnosis of acute myocardial infarction is being considered on clinical grounds."[3] This approach was recommended on the basis that troponin elevation in patients with COVID-19 is likely to be multifactorial and less likely to be attributable to atherothrombotic coronary occlusion.

Circulating cardiac troponin is a marker of myocardial injury, including but not limited to myocardial infarction or myocarditis, and the clinical relevance of this distinction has never been so clear. Clinicians who have used troponin measurement as a binary test for myocardial infarction independent of clinical context and those who consider an elevated cardiac troponin concentration to be a mandate for invasive coronary angiography must recalibrate. Rather than encouraging avoidance of troponin testing, we must harness the unheralded engagement from the cardiovascular community attributable to COVID-19 to better understand the usefulness of this essential biomarker and to educate clinicians on its interpretation and implications for prognosis and clinical decision making.

Whereas the interpretation of high-sensitivity cardiac troponin concentrations undoubtedly can cause frustration to those who long for a disease-specific biomarker for myocardial infarction, there is an opportunity here. With COVID-19 infection, mortality rates are highest in older patients (14.8% in those >80 years of age) and in patients with a history of underlying cardiovascular disease.[1] In a cohort of 191 patients with confirmed COVID-19 based on SARS-CoV-2 RNA detection, the univariable odds ratio for death when high-sensitivity cardiac troponin I concentrations were above the 99th percentile upper reference limit was 80.1 (95% CI, 10.3–620.4; $P<0.0001$).[4] This was higher than the odds ratios observed for all other biomarkers tested, including D-dimer and lymphocyte count. A study of 416 hospitalized patients with COVID-19 reported that cardiac troponin concentrations

Key Words: coronavirus ■ COVID-19 ■ severe acute respiratory syndrome coronavirus 2

https://www.ahajournals.org/journal/circ

were elevated in 1 of 5 patients at presentation. These patients were more likely to require invasive or noninvasive ventilation (22% versus 4% and 46% versus 4%) and to develop acute respiratory distress syndrome (59% versus 15%) or acute kidney injury (9% versus 0%; $P<0.001$ for all). The observed rate of mortality was 10-fold higher in patients with myocardial injury on presentation (51% versus 5%; adjusted hazard ratio, 3.41 [95% CI, 1.62–7.16]).[5]

If clinicians are reluctant to measure cardiac troponin in these patients, the consequence may be to ignore the plethora of ischemic and nonischemic causes of myocardial injury related to COVID-19 (Figure), which may be directly or indirectly associated with poor outcomes. Early recognition could facilitate appropriate triage to a high-intensity or critical care area; improve our understanding of the systemic consequences of COVID-19; and inform the use of inotropes, vasopressors, and diuretics in patients with significant cardiac dysfunction. Furthermore, testing may identify patients with a clearly defined cardiac phenotype with therapeutic implications. For example, it has been suggested that patients with myocarditis associated with COVID-19 may benefit from therapies such as a combination of immunoglobulin and corticosteroid therapy.

Elevated cardiac troponin concentrations are common in hospitalized patients and are as likely to be attributable to nonischemic causes of myocardial injury or type 2 myocardial infarction (myocardial oxygen supply–demand imbalance) as a consequence of an acute coronary syndrome. Whereas these patients are at increased risk of future cardiovascular events and may have underlying coronary artery disease, they do not have acute atherothrombosis, and there is no established role for dual antiplatelet therapy, anticoagulants, or early coronary angiography. In a situation in which the majority of hospitalized patients may be affected by COVID-19 and have significant respiratory compromise, the prevalence of nonischemic myocardial injury and type 2 myocardial infarction is likely to increase.

In critically unwell patients, oxygen supply–demand imbalance does not affect the myocardium exclusively and likely occurs at a cellular level in the majority of organ systems. However, it is the sensitivity of cardiac troponin testing that ensures it is one of the earliest and most precise indicators of end organ dysfunction. Cardiac troponin testing could prompt early initiation of measures to improve tissue oxygenation and perfusion.

Cardiac troponin testing in patients with COVID-19 could increase the need for cardiology consultation

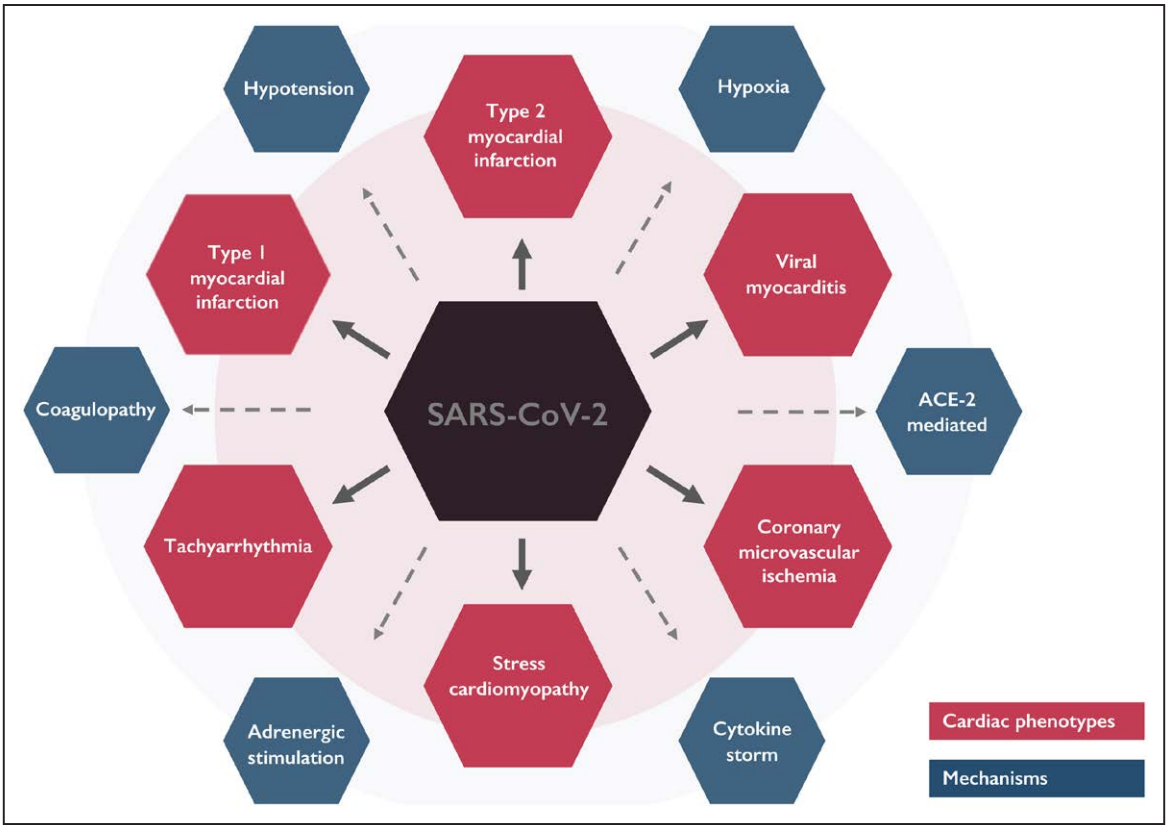

Figure. Potential mechanisms of acute myocardial injury in coronavirus disease 2019 (COVID-19) and related cardiac phenotypes.
Potential mechanisms of myocardial injury in COVID-19 and related cardiac phenotypes include viral myocarditis, coronary microvascular ischemia mediated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding of the endothelial angiotensin-converting enzyme 2 (ACE-2) receptor, or stress cardiomyopathy and tachyarrhythmia attributable to endogenous or exogenous adrenergic stimulation. Type 1 myocardial infarction attributable to atherothrombosis may be triggered by the proinflammatory and prothrombotic state. Type 2 myocardial infarction is more likely in patients with prolonged myocardial oxygen supply or demand imbalance with hypoxia, hypotension, or tachycardia.

and downstream testing, including bedside echocardiography and angiography. However, the recognition of normal or modestly elevated troponin could conversely reduce the need for cardiac imaging and minimize the risk of exposure to cardiac physiology staff. The role of further investigation must be considered carefully and based on risk to the individual performing the test and the likelihood of informing clinical management. Whereas the decision to undertake coronary angiography with appropriate personal protective equipment may be straightforward in a patient with regional ST-segment elevation and symptoms of myocardial ischemia, distinguishing pulmonary edema from acute respiratory distress syndrome may be more challenging. In this setting, cardiac biomarkers—such as high-sensitivity cardiac troponin and NT-proBNP (N-terminal pro-BNP)—may be informative and certainly require further evaluation.

Although it is prudent to act with caution, it is likely that the studies published to date have overestimated the prevalence of myocardial injury. Troponin testing was available in 145 of 191 (75%) patients included in a report drawn from 813 consecutive adults admitted to Jinyintan Hospital or Wuhan Pulmonary Hospital[4] and in 416 of 645 (64%) consecutive patients admitted to Renmin Hospital of Wuhan University.[5] It is likely that cardiac troponin measurements were requested in those who were more unwell or where there was reasonable suspicion of myocardial ischemia or myocardial dysfunction. Only systematic testing of both symptomatic and asymptomatic patients infected with SARS-CoV-2 will provide an accurate estimate of the prevalence of myocardial injury in COVID-19.

Clinicians must recognize that troponin is not a test for myocardial infarction, and it never was. No biomarker has ever had the ability to detect acute atherothrombotic occlusion in a coronary artery. This myth has been perpetuated in clinical practice, and it limits our ability to evaluate and triage care in critically unwell patients. We need more information to guide the international response to the COVID-19 pandemic. Taken together with clinical assessment and ECG, elevations of cardiac troponin can inform the diagnosis of a number of cardiac conditions related to COVID-19. We must take advantage of all available prognostic markers to identify patients with important systemic consequences of COVID-19 and determine those at highest risk of adverse outcomes as early as possible. Troponin should be considered an ally and a crucial diagnostic and prognostic aid in healthcare provision worldwide.

ARTICLE INFORMATION

Correspondence

Nicholas L. Mills, MD, PhD, British Heart Foundation Centre for Cardiovascular Science, Chancellors Building, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, United Kingdom. Email nick.mills@ed.ac.uk

Affiliations

British Heart Foundation Centre for Cardiovascular Science (A.R.C., A.B., N.L.M.) and Usher Institute of Population Health Sciences and Informatics (N.L.M.), University of Edinburgh, United Kingdom.

Acknowledgments

Dr Chapman receives support from a Starter Grant for Clinical Lecturers from the Academy of Medical Sciences (SGL021/1075). Drs Bularga and Mills received funding from a scholarship (CH/09/002) and from the Butler Senior Clinical Research Fellowship (FS/16/14/32023), both from the British Heart Foundation.

Sources of Funding

Drs Chapman, Bularga, and Mills are supported by British Heart Foundation Research Excellence Award (RE/18/5/34216).

Disclosures

Drs Chapman and Bularga have no declarations of interest. Dr Mills has received honoraria from Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, and LumiraDx. The University of Edinburgh has received research grants from Abbott Diagnostics and Siemens Healthineers.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019 in China [published online February 28, 2020]. *N Engl J Med*. doi: 10.1056/NEJMoa2002032. https://www.nejm.org/doi/full/10.1056/NEJMoa2002032
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention [published online February 24, 2020]. *JAMA*. doi: 10.1001/jama.2020.2648. https://jamanetwork.com/journals/jama/fullarticle/2762130
3. Januzzi JL. Troponin and BNP use in COVID-19. https://www.acc.org/latest-in-cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19. March 18, 2020. Accessed April 6, 2020.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China [published online March 25, 2020]. *JAMA Cardiol*. doi: 10.1001/jamacardio.2020.0950. https://jamanetwork.com/journals/jamacardiology/fullarticle/2763524