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Cardiac Troponin Testing in Patients with COVID-19: A Strategy for Testing and Reporting Results

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Abstract

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged late in 2019 causing COVID-19 (coronavirus disease-2019) may adversely affect the cardiovascular system. Publications from Asia, Europe and North America have identified cardiac troponin as an important prognostic indicator for patients hospitalized with COVID-19. We recognized from publications within the first 6 months of the pandemic that there has been much uncertainty on the reporting, interpretation, and pathophysiology of an increased cardiac troponin concentration in this setting.

Content

The purpose of this mini-review is: a) to review the pathophysiology of SARS-CoV-2 and the cardiovascular system, b) to overview the strengths and weaknesses of selected studies evaluating cardiac troponin in patients with COVID-19, and c) recommend testing strategies in the acute period, in the convalescence period and in long-term care for patients who have become ill with COVID-19.

Summary

This review provides important educational information and identifies gaps in understanding the role of cardiac troponin and COVID-19. Future, properly designed studies will hopefully provide the much-needed evidence on the path forward in testing cardiac troponin in patients with COVID-19.

Introduction

Cardiac troponin (cTn) is the recommended biomarker to identify myocardial injury and, in the correct clinical setting, myocardial infarction (MI) (1,2). The clinical utility of cardiac troponin I or T (cTnI, cTnT) extends beyond diagnosis, with an emerging role in risk stratification for patients with symptoms suggestive of acute coronary syndrome (ACS), patients in heart failure, and in patients with stable cardiovascular disease (3). Over the past several decades, data have emerged that systemic infection can trigger cardiac events (4,5). This review will present current evidence and limitations of cTn testing in patients with coronavirus disease-2019 (COVID-19).

The first severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) was identified in a proportion of human heart samples from patients who died during the Toronto SARS outbreak (6). Among the 20 patients that died, 7 (35%) had SARS-CoV in their hearts. Patients with SARS-CoV in the heart had lower levels of the SARS-CoV receptor angiotensin converting enzyme 2 (ACE2) expression in the heart and earlier mortality. This finding, as well as findings from a mouse model of SARS-CoV viral infection indicated that the impaired ACE2 system and local viral replication in the heart were playing an important role in myocardial inflammation, and that cardiac involvement was possibly contributing to the high mortality rate among patients over 65 years of age observed during the SARS outbreak (6). SARS-CoV-2, which emerged in 2019, shares approximately 80% sequence homology with SARS-CoV, and this virus also binds to ACE2 for cell entry with the TMPRSS2 membrane protease aiding in this process (7). The ACE2 protein is a transmembrane protein, which converts angiotensin II (1-8) to

angiotensin 1-7 and is an important counter regulator to the renin-angiotensin system with additional important roles in immune modulation (7). However, unlike SARS-CoV, at the time of writing this mini-review it is unknown if SARS-CoV-2 can proliferate in the heart and to what extent cTn increases observed in some patients are due to myocardial infection or some other pathophysiological event (7,8). What is evident, however, is that patients with COVID-19 may present with various cardiovascular presentations (e.g., chest pain and ST elevation, cardiogenic shock, heart failure, right ventricular stress, arrhythmia, myopericarditis, myocardial supply-demand mismatch) as well as vascular dysfunction (e.g., pulmonary embolism, deep vein thrombosis) (9-11). Myocardial injury is due to type 1 MI, type 2 MI, myocarditis, cardiomyopathy, microvascular dysfunction, arrhythmias, coagulopathies, and cytokine storm (11,12), and such injury is detected by measurement of cTn. Accordingly, if structural damage has occurred as evidenced by detection of an increased cTn, then subsequent monitoring of cTn and other biomarkers such as the natriuretic peptides or imaging may provide additional utility in this setting (13).

Cardiac Troponin and Patients with COVID-19

In an initial report from *The Lancet* on 191 patients hospitalized with COVID-19 in Wuhan, China, the most common sequelae of this infection were sepsis, respiratory failure and acute respiratory distress syndrome (ARDS) (14), as with the first (SARS) coronavirus epidemic (15). Following respiratory complications, cardiac complications were the next most prevalent finding (14). Specifically, an increased cTn based on a 28 ng/L threshold using a high-sensitivity (hs) cTnI (hs-cTnI) assay at hospital admission

had the greatest association with in-hospital death (odds ratio 80; 95% confidence interval [CI]: 10-620) (14). Unfortunately, the manufacturer of the hs-cTnI assay used was not listed, nor whether the 28 ng/L cutoff represented the 99th percentile upper reference limit (URL) for this assay.

Zhou and colleagues also identified older age, a high sequential organ failure assessment (SOFA) score, and high D-dimer concentrations at hospital admission as important independent risk factors for subsequent mortality in patients with COVID-19 (14). These data may help to inform physicians regarding which patients are at high-risk of adverse events. Unfortunately, the authors did not provide data on which variables or laboratory tests measured at hospital admission were associated with a lower risk of death. Specifically, the author excluded some clinical chemistry tests from the multivariable model, such as hs-cTnI, but not others, such as creatinine and bilirubin (bilirubin is a variable in the SOFA score), based on these tests being “unavailable in emergency circumstances”. This reason for test exclusion is surprising because a cardiac biomarker test is needed when evaluating patients with possible acute coronary syndrome in the emergency setting. Importantly, cTn should be measured, with hs-cTn assays preferred, when myocardial injury is suspected in the emergency setting (1).

Details regarding analytical performance aspects and cutoffs for cTn are important for interpretation. Unfortunately, the manuscript by Zhou and colleagues is not the only one which excluded cTn in modeling, and/or failed to list analytical performance aspects. For example, in a paper addressing 257 critically ill adult patients with COVID-19 in New York City, the median hs-cTnT concentration within 72 hours from admission was 19 ng/L (interquartile range: 9-52 ng/L) (16). Despite nearly half of the population

having myocardial injury, hs-cTnT was not included in the final multivariable model to avoid overfitting, whereas D-dimer and interleukin-6 were included (16). The multivariable hazard ratios for in-hospital death for interleukin-6 and D-dimer were modest at 1.1, whereas a history of chronic cardiac disease was higher at 1.8 (16). In other population-based studies in the acute setting outside of ACS (e.g., acute heart failure), increased cTn concentrations at presentation, but not prior MI or angina, were associated with higher mortality (17). In contrast to more subjective variables such as historical elements, assessing objective variables in the acute setting, such as hs-cTnT or hs-cTnI may be a more reliable and powerful prognostic indicators.

Two small studies showed that, next to acute respiratory distress syndrome, cardiac injury/organ dysfunction may be the second most prevalent critical condition in hospitalized patients with COVID-19 (18,19) as manifested by increased cTn at hospital admission in a large proportion. However, precise estimates on the prevalence of injury were not provided from these initial important reports. The 99th percentile from a healthy population is globally recommended as the cTn URL cutoff, with different manufacturers having different URL cutoffs (1,20,21). In this regard, Arentz and colleagues report 3 of 21 critically ill patients in Washington state with cTn > 0.3 µg/L, however, the cTn assay manufacturer is not listed in this report and it is unclear if 0.3 µg/L is the 99th percentile URL or a local cutoff for a contemporary cTn assay (18).

Wang and colleagues also do not report the name of the manufacturer of the hs-cTnI assay in their manuscript. However, they list an overall cutoff of 26.2 ng/L, which likely indicates the assay is manufactured by Abbott Diagnostics (19,20) Here, one can estimate that approximately 25% of patients admitted to the intensive care unit in

Zhongnan Hospital, Wuhan, China had cardiac injury using this overall cutoff (19). However, this assay has a higher URL for men (34 ng/L) and a lower one for women (16 ng/L), so that it is probable that the prevalence of injury in this study was underestimated for women and overestimated for men (22).

In another study Shi and colleagues demonstrated in a large consecutive patient cohort with COVID-19 that myocardial injury, identified at admission, was associated with a higher risk of in-hospital mortality (23). Specifically, in 416 patients hospitalized with COVID-19 in China, 82 had an initial cTnI above the URL suggesting approximately 20% of the cohort had evidence of myocardial injury. Those with increased cTnI, compared to those without, developed more severe disease on multiple measures, including mortality: 42 of 82 (51.2%) vs 15 of 334 (4.5%). Those with increased cTnI had many more cardiac comorbidities and by Cox regression modelling cardiac injury was independently associated with a higher risk of death, both during the time from symptom onset (hazard ratio, 4.26 [95%CI, 1.92-9.49]) and from admission to the end point (hazard ratio, 3.41 [95%CI, 1.62-7.16]) (23).

The authors indicated that a hs-cTnI assay was used in the study, but no data or references were provided. It is important that the correct terminology and reporting units be used when reporting the type of cTn assay (1); this is a common important limitation in the methods in clinical journals (24). Here, the recommended unit for hs-cTn assays is ng/L; units of ng/mL or µg/L are discouraged to prevent misinterpretation and reporting errors (1,2). Reviewing the reporting units for the cTnI results in Shi and colleagues' study, it would appear that the Siemens ADVIA Centaur TnI-Ultra assay was used with the lower reportable limit being 0.006 µg/L and overall 99th-percentile being 0.04 µg/L

(20). This cTnI assay would be classified as a contemporary assay and not a high-sensitivity assay. The actual hs-cTnI assay from Siemens reports in ng/L and received regulatory approval in 2018 in the United States (ADVIA Centaur XP/XPT hs-TnI with a lower reportable limit being 2.5 ng/L, with the female 99th percentile URL being 40 ng/L and the male 99th percentile URL being 58 ng/L) (20). The actual cTnI assay used in Shi's study was not reported in the paper (23). In a randomized clinical trial, the maximum concentration of hs-cTn for COVID-19 patients randomized to colchicine or not was likewise omitted (25). In this trial, not only were the units reported as ng/mL (with 4 decimal places), but it was also not specified if one or several hs-cTnI or hs-cTnT assays were used, and there were no analyses performed on differences in incidence of myocardial injury using the 99th percentile cutoffs (25).

Guo and colleagues studied 187 patients admitted with COVID-19 (26). Mortality was 7.6% for those without cardiovascular disease (CVD) and a normal cTnT, and up to 69% for those with CVD and just a single increased cTn. In those who died (n= 43), cTn (and NT-proBNP) concentrations rose steadily throughout hospitalization; for those who survived (n= 144), the levels remained at a plateau (26).

In another publication, of 3069 patients hospitalized in five New York medical centers between February 27 and April 12, 2020, 2736 patients had at least one cTnI (URL <0.03 µg/L) measured within the first 24 hours (27). Here, 1751 patients (64%) had an initial cTnI within the normal range (27). The median age was 66 years; with nearly 41% over the age of 70 years, and 60% of the cohort being men. Cardiovascular disease was more prevalent in those with higher cTnI concentrations. Higher cTnI correlated with more history of heart failure, diabetes, and hypertension, as well as higher

D-dimer, and nearly all inflammatory markers. An initial cTnI result between 0.03 µg/L and 0.09 µg/L (n = 455, 16.6%) had adjusted hazard ratio for death of 1.75 (1.37-2.24), and cTnI > 0.09 µg/L (n= 530, 19.4%) was associated with HR of 3.03 (2.42-43.08) (**Fig. 1**) (27). However, the authors do not report whether the cTnI in question was the initial cTnI, the peak cTnI, or whether more than one cTnI was measured in this cohort (27).

Furthermore, in a small meta-analysis, it was evident that an increased cTn was associated with increased severity and mortality in patients with COVID-19 (28). The mechanism of myocardial injury associated with COVID-19 is not certain, and as alluded to above could be due to ACS, myocarditis, direct damage from inflammatory mediators/cytokines, microvascular damage, type 2 MI due to hypoxia or tachycardia, microvascular damage due to diffuse intravascular micro-thromboses, direct entry of SARS-CoV-2 into myocytes by using ACE2 receptors, or other unknown mechanisms.

Again, assay details are important, especially with regard to hs-cTn assays where risk cutoffs below the 99th percentile URL as well as sex-specific 99th percentile URLs are recommended (1-3). Of note, Shi and colleagues also published another larger, all consecutive patient cohort with COVID-19 (n=607 patients) in which cTnI testing was performed with the Siemens ADVIA Centaur XP analyzer (with 0.04 µg/L as the URL cutoff) (29). However, they made no reference to the assay being a hs-cTn assay (contrary to their other publication) despite submitting the *European Heart Journal* manuscript one week before their *JAMA Cardiology* paper was accepted for publication (23,29).

With the COVID-19 pandemic encompassing more and more countries, the data and expert opinions suggest that myocardial injury in this clinical setting portends a

short-term considerable risk (11, 30). However, the importance of the details of cTn assays cannot be overemphasized, as cTnI and cTnT concentrations in the blood can vary up to 20-fold because of the lack of assay standardization, as capture and detection antibodies used in assays differ by manufacturer, and they do not all recognize the different forms of cTn or degradation products (31). Lack of between-assay calibration is a well-known problem that has no solution. Thus, professional societies have recommended that each cTn assay manufacturer determine their own unique 99th percentile URLs in an appropriate healthy population (1). It is unfortunate that the studies on patients with COVID-19 have not conformed to the international guidelines concerning cTn assays and this shortcoming hampers the ability to interpret the current clinical outcomes data. Proper classification, reporting and interpretation of the cTn concentrations derived from hs-cTnI or hs-cTnT assays, which have better analytical precision and accuracy compared to contemporary assays, likely would provide improved clinical utility in patients with COVID-19. In this regard, a more systematic approach in testing and interpreting hs-cTn results in COVID-19 patients is needed pertaining to the following questions: a) when and how often to measure cTn, b) what serial changes in cTn concentrations are informative, c) whether risk cutoffs or sex-specific URLs should be used in this setting, d) whether the clinical utility of the cTn result improves if interpretation is based on time from infection, symptom onset or hospital admission ?

Testing strategies

Data on acute myocardial injury associated with COVID-19 show a very strong independent association between increased cTn concentrations and disease severity,

including mortality, and a correlation of increasing severity with increasing cTn concentrations. Notwithstanding the absence of pertinent information on cTn testing in the initial reports of patients with COVID-19, data do indicate that myocardial injury and likely type 2 MI are important diagnoses that affect mortality outcomes in this population. Type 2 MI, caused by an oxygen supply and demand mismatch rather than a coronary atherothrombosis (2), as well as any other myocardial injury pathophysiologies, is associated with higher subsequent mortality in both the emergency department population and in hospitalized patients (5, 32, 33). In patients with COVID-19, there also are reported increases in inflammatory biomarkers (8,11) which may or may not be responsible for the cardiac dysfunction observed in this group (34). In critical care patients, it is evident that an increased cTn concentration on admission does identify those at high risk and is perhaps related to underlying cardiovascular comorbidities and their severity of illness (e.g. high SOFA score) (35). However, in assessing patients with COVID-19 and for patient management and resource allocation in an emergency situation, a continuum of risk even at low hs-cTn concentrations might be informative to identify individuals at greater risk before cTn concentrations increase above the 99th percentile URLs (3,36). Important questions persist in the application of hs-cTn testing for risk stratification of patients with COVID-19; specifically, can interventions targeted to hs-cTn monitoring guide management and improve patient outcomes?

Another unknown is the trajectory of hs-cTn in the convalescent period following discharge of patients with COVID-19: is there an increase, decrease or no appreciable change in hs-cTn concentrations? Other populations have indicated that there is a period of remodeling in which cTn may be increased (37). Is this also true for COVID-19

patients who have recovered and who no longer have detectable SARS-CoV-2 virus? Moreover, should testing in this setting be only for patients with COVID-19 and myocardial injury or any patient infected with SARS-CoV-2, since ACE2, the receptor for the virus, is also expressed biologically in the heart (6-8). If cTn continues to be increased in the convalescent period, what are the implications for management, including further testing, prognosis, follow-up with cardiology, or further therapy? (37,38) Here, initial data using cardiovascular magnetic resonance (CMR) in 100 patients recovered from COVID-19 revealed abnormal CMR findings and detectable hs-cTnT concentrations in over 70% of the population with 1 in 20 patients having hs-cTnT ≥ 14 ng/L (13). For cTn measurements obtained *following* resolution of the illness to be informative cTn monitoring *during* the illness may be required for appropriate interpretation; testing with comparison to appropriate controls should be carried out over subsequent months to evaluate if concentrations have stabilized, decreased, or even increased after the virus has cleared. cTn measurement would need to be performed using the same hs-cTn assay/methodology for accurate interpretation, as differences between assays are evident even in the low concentration range (39). To avoid any misinterpretation of cTn concentrations, patients here would be advised to go to the same outpatient setting that uses the same cTn assay that was tested during their acute illness. Properly conducted studies in this setting are needed to address these issues.

Such studies would require long-term testing with hs-cTn in patients who have been infected with the virus. Data have indicated that increased concentrations of both hs-cTnI and hs-cTnT are associated with future heart failure and cardiovascular disease death in both stable and high-risk older populations (38,40). There may be subtle

differences in observed increases between cTnI and cTnT, with cTnI possibly more specific for future coronary heart disease and with cTnT more strongly associated with non-cardiovascular death (40). At present, it is not known whether screening with hs-cTnI and/or hs-cTnT would be helpful in the COVID-19 population for subsequent risk stratification to mitigate possible future cardiovascular outcomes. It is also unknown if patients infected with SARS-CoV-2 are at greater long-term risk for cardiovascular outcomes, so an objective assessment via measurement of hs-cTn may be helpful as a proactive measure for prevention.

Fortunately, the vast majority of patients with COVID-19 appear to eventually recover from their acute disease. It is likely that the high number of increases in cTn concentrations that are seen in COVID-19 patients reflect critical illness, although the interaction with the heart and SARS-CoV-2 may have an important role in some patients. As we acknowledge, increased cTn does not, however, guide any treatment strategies to minimize myocardial injury. For this reason, initial opinions suggested that it should not be measured in patients unless acute MI is on the differential diagnosis. However, utilizing a test, such as hs-cTn testing (**Table 1**), may provide important adjunct information in the acute setting, with a promise for future utility in cardiovascular health risk stratification over both the short- and long-term. Further, when the ECG is nondiagnostic for coronary occlusion, or the patient is suspected of having a non-occlusion MI, consider echocardiography to inform the decision for angiography. Because cTn is a biomarker of disease severity and a powerful independent predictor of adverse outcomes, it may be quite useful in the emergency department disposition

decision, and if cTn is found increased and the patient not admitted, then outpatient management should be considered.

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Table 1. Recommendations (and rationale) for cardiac troponin reporting

<p>1. Indicate the name of the manufacturer and instrument/device used for cTn measurement</p> <p><i>Rationale: Concentrations will be different between different devices and manufacturers</i></p>
<p>2. Provide the analytical measuring range of the cTn assay, indicating important low end parameters such as the limit of detection or limit of quantification and precision data</p> <p><i>Rationale: Is important when assessing if an assay is a hs-cTn assay</i></p>
<p>3. Indicate the URLs, as one overall cutoff is recommended for contemporary cTn assays, whereas sex-specific URLs are recommended for hs-cTn assays</p> <p><i>Rationale: Different cTn assays will have different URLs and should have reference/data to support the chosen URLs</i></p>
<p>4. Provide details on what sample type was used for the measurement, storage conditions, and when was the sample collected (i.e., time from onset, hospital presentation, hourly, daily etc.)</p> <p><i>Rationale: Different sample types, pre-analytical variables including sample handling and storage can affect cTn results. Interpretation is best when details regarding when the samples were collected for measurement are provided</i></p>
<p>5. Report hs-cTn in ng/L units and contemporary cTn in ug/L units</p> <p><i>Rationale: Reduces confusion on type of assay used and possible misinterpretation of results</i></p>

Figure 1. Cardiac troponin and risk of death in patients hospitalized with COVID-19

(Modified with permission from reference 27).

