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Commentary on Macrotroponin Complex as a Cause for Cardiac Troponin Increase after COVID-19 Vaccination and Infection

Bernard Croal[a,*]

Since the existence of potential macrotroponin complexes was first mooted in 2011 (1), further parallel work has highlighted a variety of possible causes of assay interference that may occur in a wide spectrum of clinical presentations where a troponin test request is clinically indicated. It remains unclear as to the precise mechanisms that lead to such interference and how troponins I versus T are affected, as well as the apparent increased involvement for certain assays, notably the high sensitivity troponins (2).

Clinically, any interference in a troponin assay measurement can produce spurious results that can lead to inappropriate diagnosis and subsequent management errors with suboptimal outcomes for the patient. Additional consequences for the patient's recorded healthcare status and insurance risk may also be significant.

This series of cases focusing on patients following COVID-19 vaccination and infection adds a modern and relevant twist, so it would be important to publicize this at the present time given the significant burden that

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COVID-19 infection and possible vaccine reactions continue to impose on healthcare systems around the world. Acute presentations of potential acute coronary syndrome or myocarditis related to, or in the context of, COVID-19 infection or vaccination should, as suggested, consider assay interference when increased troponin levels are discordant with clinical or other investigations. Given that many emerging clinical guidance protocols may also suggest the use of tests such as troponin or natriuretic peptides in the assessment of patients with long COVID following the acute sequelae SARS-CoV-2 infection, then caution should also be observed in interpreting such test results in these patients.

Further work is now indicated to improve the knowledge surrounding interfering factors including prevalence in different clinical scenarios, clinical significance, and development of consistent, standardized approaches for identification and interpretation. Clarity around the prevalence and nature of immunoassay interference in these patient groups is crucial for their future management.

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Commentary on Macrotroponin Complex as a Cause for Cardiac Troponin Increase after COVID-19 Vaccination and Infection

Peter A. Kavsak[a,*]

During the coronavirus disease 2019 (COVID-19) pandemic, there was renewed interest in infection, inflammation, and myocardial injury. Intriguingly, a publication from a decade ago looking at high-sensitivity cardiac troponin T (hs-cTnT) testing at 3 different biennial collection intervals in healthy children revealed that transient increases in hs-cTnT were more suggestive of an infective etiology as opposed to any cardiac disease (1). With the findings from Bularga and colleagues' clinical case study on macrotroponin following COVID-19 vaccination or infection, another possible explanation, in hindsight, for the previous hs-cTn elevations in children may be due to macrocomplexes.

There are several analytical causes for increased cTn concentrations that are incongruent with ongoing myocardial injury (2), with one being immunoglobulin bound cTn, often called "macrotroponin." Biochemical detection of macrocomplexes can be performed by either polyethylene glycol precipitation or immunoglobulin removal, as was performed in this case study. However, prior to performing such biochemical procedures, it is often helpful to assess whether the cTn elevations in serial sampling represent stable levels, where <20% change in concentrations is used for this stable designation. Intriguingly, 1 of the 3 patients in the case study exhibited a major decrease in hs-cTnI over 3–6 hours, from 280 000 ng/L to 180 000 ng/L (−36%), yet the paired hs-cTnT concentrations in these same samples were normal/unchanged at 8 ng/L and 6 ng/L, respectively.

When investigating possible macrocomplexes, testing with another hs-cTnI method may be beneficial, and here testing with hs-cTnT (another protein) further suggested an interference. However, macrocomplexes may yield different hs-cTn results on different manufacturer platforms and assay versions, with the findings from this case study also indicating that samples requiring dilutions (i.e., Abbott hs-cTnI >50 000 ng/L requires dilution) may also yield discrepant results. Careful collaboration between the

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