Your cheatin' heart

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Introduction

Troponins have taken the world by storm. In recent years we have been told that troponin assays are highly sensitive and specific, and that they predict future outcomes in patients with chest pain and acute coronary syndromes (ACS). These must be wonderful tests indeed. But the Diagnostic Challenge[1] by Katis and Dias (see page 123) illustrates the difficulty of relying too heavily on any test for clinical decision-making. As is true for all tests, the interpretation of a troponin result depends on several factors — most importantly the clinical picture (a.k.a. the pre-test likelihood of the disease in question). In this case a patient with chest pain and ST elevation is shown to have significant elevation of cardiac troponin at multiple time points, but the final diagnosis is pericarditis. This may be disconcerting for physicians who depend on troponins to distinguish ACS from other causes of chest pain. The aim of this Commentary is to review the use of cardiac troponins in the diagnosis of myocardial ischemia and to discuss possible shortcomings of the test — particularly in the context of acute pericarditis.

The diagnostic imperative

In few areas of medicine has more effort been directed at improving diagnostic accuracy than in the detection of myocardial ischemia. This is for good reason. Emergency physicians confront large numbers of patients whose symptoms are compatible with unstable angina (UA) or myocardial infarction (MI), the acute coronary syndromes. Data from the Institute for Clinical and Evaluative Sciences in Ontario[2] reveal that the one-year risk-adjusted mortality for patients admitted with MI ranges from 11.3% to 23%. The majority of deaths following MI occur in the first days after the onset of the event.[3,4] Thirty-day data for the clinical end-point of death or MI from the control arms of recent clinical trials evaluating therapy for UA indicate that this end-point is met in approximately 10% to 15% of patients.[5] The majority of these adverse events also occur early after the onset of symptoms.[4] In the case of both MI and UA, there is evidence indicating that the effectiveness of therapy is directly dependent on the time to treatment.[6–8] Thus there is tremendous pressure on emergency physicians to make a timely diagnosis of ACS and initiate appropriate therapy.

Cardiac troponins

Historically, the standard biochemical marker for myocardial injury was the creatine kinase MB isoform (CK-MB). The development of troponin I (TnI) and troponin T (TnT) assays, and a recent shift toward the use of early markers like myoglobin, have perhaps improved the diagnosis of ACS, but they have also made the evaluation of chest pain more confusing. Troponin assays appear to be highly sensitive and specific for myocardial injury.[9] In addition, positive troponin values are independent predictors of poor outcomes in the short-term[10–13] and long-term.[14,15] Angiographic studies suggest that patients with even minor elevation of troponin levels have more visible coronary thrombi and less coronary flow.[16] Indeed, the European Society of Cardiology and the American College of Cardiology have revised the definition of MI and identified troponin as the preferred biochemical marker of myocardial necrosis.[17]

Troponins for risk stratification

Because several studies have demonstrated that expensive and invasive therapies are more likely to benefit patients who have higher baseline risk, it is an attractive notion that troponin results can be used to risk stratify ACS patients and determine treatment strategies. This approach is supported by retrospective data from studies of patients with non–ST-elevation ACS, which suggest that the benefits of therapy with a glycoprotein IIb/IIIa antagonist are restricted to troponin-positive patients.[18,19] Prospectively collected data produce a more confusing picture. The authors of one recent trial (TACTICS-TIMI 18)[20] suggest that patients with any detectable troponin (not just those with levels exceed-

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ing the diagnostic threshold for MI) should be admitted to a coronary care unit, receive intravenous glycoprotein IIb/IIIa therapy and undergo cardiac catheterization. But the GUSTO IV-ACS trial,[21] the first large trial in which patients could be enrolled based on a positive troponin test, produced contradictory results. Like prior studies, it showed that troponin-positive patients had higher 30-day event rates, but it also showed no benefit of IIb/IIIa treatment — regardless of troponin level. These conflicting results may relate to different levels of patient risk in the populations studied (GUSTO-IV ACS enrolled a relatively low-risk population with an 8% rate of death or MI at 30 days) and to different rates of percutaneous intervention. Regardless, they suggest that caution is warranted in extrapolating the above findings to clinical practice and they suggest that further studies relevant to the emergency department setting are required before we can feel comfortable using troponin levels to assign expensive or invasive treatment strategies.

Non-ACS-related increases in troponin

As the routine use of troponin testing has expanded to lower-risk patient populations, it has become clear that conditions other than myocardial ischemia cause troponin elevations. Physicians cannot, therefore, assume that a positive troponin assay reflects myocardial ischemia, and they should also consider other conditions that cause troponin release. Elevated levels of cardiac troponin have been documented in myocarditis[22] and congestive heart failure, being associated with worse clinical outcomes in the latter.[23,24] It has been known for several years that troponin (particularly TnT) can be elevated in chronic renal failure. These elevations may or may not correlate with adverse outcomes.[25,26] Troponin elevations have also been observed in the setting of pulmonary embolism and, here too, appear to predict worse outcomes.[27,28] Finally, elevated troponine levels with no apparent cardiac cause have been reported in patients both in the emergency department and on general medical wards.[29–31]

A study by Kratz and cohorts[31] is particularly interesting because it compared troponin levels obtained from healthy volunteer blood donors with a group of hospital inpatients who were examined and determined not to have myocardial ischemia. The authors conclude that if the 99th percentile cutoffs derived from healthy blood donors were applied to the hospital inpatient population, a significant percentage of these (up to 13%) would have been misclassified as having ACS.

Troponins in pericarditis

The diagnosis of pericarditis is based on typical clinical features, and pericarditis may be difficult to distinguish from acute MI.[32,33] Anecdotally, this mistake may be more common than is generally appreciated. In the case described by Katis and Dias in this issue of *CJEM*, the correct diagnosis was made based on the history and the results of the ECG, although troponin elevation was consistent with MI. The combination of troponin elevation and ST elevation (in a patient with pericarditis) may lead physicians to an incorrect diagnosis and, thus, potentially harmful therapy.

It is tempting to assume that elevated levels of troponin are associated with more severe pericarditis or worse outcomes, or that this test provides additional prognostic information compared to CK-MB. The available literature suggest otherwise. In a retrospective study of 69 consecutive patients hospitalized with pericarditis, Bonnefoy and colleagues[34] found that 49% had positive troponin assays, but that length-of-stay, relapse rate and re-hospitalization rate were equal in patients with and without detectable troponin levels. Furthermore, the likelihood of adverse events in troponin-positive patients appeared unrelated to the magnitude of troponin increase. Brandt and coworkers[35] studied 14 patients with pericarditis and found that troponin levels were elevated only marginally more often than CK-MB, although these conclusions are limited by the very small sample size. Because troponin release kinetics were similar to those observed for CK-MB, the authors concluded that troponin testing added little to the assessment of pericarditis and, in particular, that it did not help to differentiate pericarditis from coronary ischemia.

Summary

While we would love to have a simple test that differentiates myocardial ischemia from other causes of chest pain, it is increasingly clear that troponin assays may be abnormal in a number of different conditions. Therefore, results must be interpreted according to the pre-test probability of the condition being tested for. The primary danger of troponin testing lays in overconfidence in test results and oversimplification of complex clinical problems. In patients with chest pain, tests cannot replace clinical judgement, and there remains no substitute for careful clinical evaluation when formulating a diagnosis or treatment plan.

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