Review Article

Cardiac troponins in the elderly: interpretation of elevated levels

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Abstract  Elderly patients with myocardial infarction commonly present with symptoms other than chest pain. The clinician evaluation of the elderly may rely on laboratory methods more so than in younger patients. Fortunately, advances in laboratory science have brought newer biomarkers of cardiac injury to the clinical arena including cardiac troponins I and T (cTnI, cTnT). These regulatory components of the contractile apparatus are sensitive indicators of myocardial injury. Their central role in the current definition of acute myocardial infarction highlights their utility in the diagnosis of acute myocardial ischemic syndromes. The troponins are also released in some clinical situations where thrombotic complications of coronary artery disease and resultant acute myocardial infarction have not occurred. Examples of these conditions include conditions like myocarditis, pulmonary embolism, sepsis, and acute stroke. Elevated troponins in these conditions are thought to emanate from injured myocardial cells and in most circumstances have been associated with adverse outcomes. Interpretation of elevated troponin in the elderly requires consideration of other possible conditions. (J Geriatr Cardiol 2007;4:188-192.)

Key Words  acute myocardial infarction; thrombolysis; elderly

Introduction

In general, medical diagnosis relies heavily on the history and physical examination augmented by diagnostic testing. Diagnosis in the elderly population may be hindered by cognitive impairment which limits obtaining a comprehensive history. Additionally, the presentation of some clinical conditions varies with age. Acute myocardial infarction is just such a condition.1, 2 Fortunately, the science of laboratory testing continues to advance with new markers entering clinical practice and more precise instrumentation reaching the market. The cardiac troponins are one such advance that has made a significant contribution to the diagnosis of myocardial injury in the elderly.

Intracellular Ca2+ triggers excitation-contraction coupling within the cardiac myocytes as interdigitated thick and thin filaments of the sarcomere slide past on another. This process is closely regulated by the troponin complex. Greaser et al. demonstrated that the troponin complex is comprised of three distinct proteins which are designated cardiac troponin T (cTnT), troponin C (cTnC), and troponin I (cTnI).3 The nomenclature for the troponin proteins refer to their functional properties (I for inhibitory, C for calcium binding, and T for tropomysin binding). The troponins were identified as the Ca2+ binding site of the myofibrillar thin filament by Ebashi et al.4 At least one epitope of the troponins is conserved across the vertebrate phyla indicating their phylogenetically antiquity.5 Each of these proteins in the troponin complex interact and serve an important function in cardiomyocyte contraction. Troponin C initiates contraction by binding Ca2+ to its N-terminal regulatory site. This binding results in a conformational change in troponin C, signaling troponin I to release its inhibition of actomyosin.6 Most of the intracellular troponin is bound to the contractile apparatus. However, a small proportion of cTnT (approximately 7%) and cTnI (3-5%) exist free in the cytosol in cardiac myocytes.7 This binding of the cardiac troponins has implications for the kinetics of troponin release. Although analogous proteins are present in other body tissues, the cardiac specificity of the troponin T and I proteins has lead to their clinical application in the diagnosis of myocardial injury.

Traditionally CK-MB had been the diagnostic marker used to confirm myocardial injury. More recent compelling clinical data demonstrated the superior performance of the troponins in the diagnosis of cardiac ischemia. These data lead the European Society of Cardiology and the American College of Cardiology to recommend replacing the traditional CK-MB with cardiac troponins as the preferred diagnostic marker for acute myocardial infarction.8

Despite the specificity of the cardiac troponins, their application to clinical practice requires an appreciation of the basics of interpreting clinical laboratory testing and the clinical conditions associated with elevations of these markers.
This is perhaps more important in the elderly where history may be less reliable. Knowledge of acute conditions other than acute myocardial infarction that may be associated with troponin release is also crucial.

Interpreting clinical laboratory tests in the elderly

Interpretation of diagnostic tests is a clinical process with its own lexicon and science. Where the performance of any laboratory test is commonly reported in terms of sensitivity and specificity. Sensitivity is defined as the percent of people with the condition in question who test positive. Similarly, specificity is defined as the percent of people free of the disease whose test result is negative. Sensitivity and specificity are not fixed characteristics of a diagnostic test. They may be affected by the population used to derive the values. High sensitivity and specificity are certainly desirable characteristics for a diagnostic test but they don’t fully describe the performance of a test in clinical practice. Sensitivity and specificity are impacted by the specific cut-off value chosen to represent a positive test. By modifying the value defined as a positive test, one could obtain many value of sensitivity desired, trading off sensitivity for specificity. The Receiver Operating Characteristic curves (ROC) are commonly constructed to more completely describe the performance of diagnostic tests through the whole range of positive cut-off values. The area under the ROC curve (c statistic) is an indicator of test performance independent of positive cut-off value. ROC curves for the cardiac troponins and other biomarkers of myocardial injury have been published for a population of patients evaluated for possible myocardial infarction. In general these markers demonstrate excellent discriminatory power.

The clinician evaluating a test result in a particular patient is really interested in the probability that a patient has or does not have the condition in question, given their test result; it is called predictive value of the test. The positive predictive value (PPV) is the probability of a patient having the disease given that his test is positive. The negative predictive value (NPV) is the probability the patient does not have the disease given that his test is negative. The predictive value of a test is dependent on characteristics of the test (sensitivity and specificity) as well as the prevalence of disease in the population.

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\text{PPV} = \frac{\text{prevalence} \times \text{sensitivity}}{\text{prevalence} \times \text{sensitivity} + (1-\text{prevalence}) \times \text{specificity}}
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Thus a positive test from a patient with very little chance of the disease will not be a strong indication of disease.

Troponins I and T in myocardial ischemia

The spectrum of acute coronary syndrome (ACS) includes ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, and unstable angina. Advancing age is a recognized risk factor for myocardial infarction is a predictor of worse outcomes. The most common substrate for ACS is an unstable atherosclerotic plaque in a coronary artery that ruptures and exposes thrombogenic material to the blood stream leading to thrombotic obstruction of the vessel. The cardiomyocytes, deprived of vital substrate, develop ischemia. Prolonged ischemia of sufficient severity (10 to 20 minutes in animal models) leads to myocytic death and the release of biomarkers of cell injury including troponins I and T.

The traditional diagnosis of myocardial infarction (MI) required fulfilling at least two of three World Health Organization criteria: (1) typical symptoms, (2) typical ECG changes, or (3) elevated levels of CK-MB. The development of more sensitive and specific biochemical markers of cardiomyocyte death like the troponins revealed that approximately ½ of patients not meeting the WHO criteria for MI test positive for cardiac troponin indicative of myocardial necrosis. This observation lead to the revised definition of MI using troponin elevation beyond the 99th percentile of an apparently healthy population. This redefinition of MI has lead to more ACS patients being assigned the diagnosis of MI. Concern that this new definition was labeling low risk patients as MI have been assured by numerous studies confirming adverse prognosis among those patients meeting the revised definition of MI. Even very low-level elevations of troponin have clinical relevance. In the TACTICS-TIMI 18 trial, elevations of cTnI just above the 99th percentile for the assay were associated with a tripling of the risk of recurrent MI or death.

Cardiac troponins in myocarditis and pericarditis

Myocarditis is an acute inflammatory process that damages myocytes and releases CK-MB as well as cardiac troponins. Patients with pericarditis also often have involvement of the epicardium with myocyte injury. cTnI is elevated in approximately 1/3 of these patients. These conditions must be considered in the elderly with elevated troponins as they may present with precordial chest pain and mimic much of the clinical presentation of myocardial infarction, including regional wall motion abnormalities.

Cardiac troponins in heart failure

The prevalence of elevated cTnI was determined for a cohort of heart failure patients without acute myocardial infarction or myocarditis by Horwitch et al. Two hundred thirty eight patients with advanced heart failure referred for transplant evaluation were studied Baseline cTnI elevations were found in 49.1% of the population (mean 0.24 ± 1.08 ng/ml) These patient by some measure were sicker than cTNI nega-
Cardiac troponins in pulmonary embolism

Venous thromboembolism resulting in pulmonary embolism can increase right ventricular wall stress and lead to right ventricular microinjury. Release of troponin has been described under these circumstances. These troponin leaks are typically small but appear to correlate with the level of right ventricular dysfunction and portend a worse prognosis. Nonetheless, troponin release has prognostic implications. Pruszczzyk et al. reported on a cohort of 64 patients with proven pulmonary embolism who presented with normal systemic arterial pressures. Half of the population had elevated troponin levels and all 8 in-hospital deaths came from this population. A positive troponin test was the only significant predictor of adverse outcome in a multivariate analysis. cTnT may be preferable to echocardiography and may provide additional prognostic data.

Cardiac troponins in renal insufficiency

CK and CK-MB may be increased in some patients with chronic renal insufficiency. This becomes an issue when you recognize the high prevalence of coronary artery disease in patients with end-stage renal disease, and their high annual cardiovascular death. At least some chronic renal disease patient not thought to have cardiac ischemia have elevations of serum troponins. These elevated troponin levels predict short term prognosis even in patients without ACS. Reduced renal clearance is not the likely mechanism of elevated troponins in renal insufficiency as these molecules are large with extra-renal clearance mechanisms. Elevated troponins in this population may be the result of ongoing myocyte damage. There is some pathologic support for the presence of micromyocardial infarction which might be clinically silent and associated with increased risk of death.

Cardiac troponin elevation in sepsis

Sepsis is another condition that may lead to elevations of cardiac troponins. Spies et al. in a population of surgical intensive care unit (ICU) patients, reported on cTnT levels in a group of 26 septic patients. Sixty nine percent of septic patients in their study were positive for cTnT based on their criteria. Baseline characteristics or the cause of sepsis did not explain the cTnT elevations. Mortality was double in the troponin positive group. In another small study of sepsis and septic shock patients, Ammann et al. reported a prevalence of cTnI positivity of 85% shock. Myocardial contractility depression is commonly found in septic patients. The cause of myocardial dysfunction in sepsis is not entirely clear, but cytokine production and release of intracellular mediators likely play a role. It is possible these same mechanisms lead to troponin release in a subset of septic patients.

Cardiac troponin in mixed critical care patients

Mortality of adult patients admitted to the intensive care unit is related to organ dysfunction, including cardiac dysfunction. These patients are at increased risk for cardiac ischemia because of underlying coronary artery disease, increased tissue oxygen demands, tachycardia and other factors. Twenty one percent of a cohort of 260 patients admitted to an adult ICU had recognized cardiac dysfunction including MI, unstable angina, and CHF. These patients were significantly older and had higher probability of developing multiorgan dysfunction, clinically recognized cardiac dysfunction, pulmonary dysfunction, vascular thrombosis, and severe sepsis or septic shock were independently associated with hospital mortality. Oscarsson et al. prospectively evaluated a population of 546 elderly patients undergoing non-cardiac surgery. cTnT was measured on the 5th and 7th postoperative days and patients were followed for 1 year. The occurrence death and non-fatal cardiac events were ascertained. These authors found that 9.7% of patients had elevated cardiac cTnT. Only 11% of these cTnT positive patients had electrocardiographic or clinical signs of ischemia. An elevated cTnT was associated with a 14.9 fold increase in the risk of mortality in the first year post operation.

Arlati et al. examined a group of patients with sepsis, septic shock, and hypovolemic shock. cTnI was elevated in 74.2% of the patients and was found to correlate with the degree of hypotension in the cohort. In another cohort of 58 critically ill patients without acute coronary syndrome as reported by Ammann et al, cardiac troponins were positive in more than ½ of patients and were associated with an increased risk of mortality. Systemic inflammatory response syndrome, sepsis or septic shock patients were even more likely to have elevated troponin (63%).

Cardiac troponins in acute stroke

Acute stroke is a leading cause of death in Western civilization and is associated with significant disability. The elderly experience a disproportionate burden from stroke as the incidence of this disorder double for every decade over age 55. CK-MB elevations have been previously reported
following acute stroke and identified as having prognostic value. In an observational study of 181 consecutive stroke patients admitted to the medical service of Auckland Hospital, cTnT levels were elevated in 17%. Forty percent of these patients died ac compared to 13% of the cTnI negative patients (RR 3.2). IN a multivariate model include historical factors such as the presence of ischemic heart disease and diabetes mellitus, smoking and impaired renal function, as well as measures of stroke severity. Only altered level of consciousness at presentation and elevated cTnT were predictive of mortality. In this study clinical severity of stroke or CT based severity. Chalala et al. did report an association between NIH Stroke Scale and elevated cTnT in a retrospective study of 160 acute stroke. cTnI elevations occurred in 10 patients, two of whom had ECGs suspicious of ischemia.

These troponin elevations are thought to be the result of cardiomyocyte damage which is neurally mediated through abnormal autonomic activity. However, clinicians faced with an elderly stroke patient must always consider co-existent acute coronary syndrome.

Cardiac troponins in percutaneous coronary interventions (PCI)

The use of percutaneous coronary revascularization procedures for acute myocardial infarction and other manifestations of coronary disease has increased exponentially. It is quite common to have elevated troponin measurements after PCI. Large increases in markers of myocardial injury are prognostic in PCI patients. Greater increases portend a worse prognosis: a normal CK-MB post procedure was associated with a mortality of 7.5%, elevations up to 3 times the upper limit with a mortality of 8%, elevations 3-5 times the upper limit with a mortality of 11%, elevations 5-10 times the upper limit with a mortality of 10.8%, and elevations > 10 times the upper limit with a mortality of 29.3%. These troponin elevations are thought to be the result of cardiomyocyte damage which is neurally mediated through abnormal autonomic activity.

Conclusions

The cardiac specific troponins are sensitive and specific markers of myocardial injury that may play an even more important role in the clinical diagnosis of elderly patients. They are elevated in many clinical syndromes associated with direct myocardial injury, myocardial ischemia, or ventricular strain. The clinician must determine whether an elevation in troponin level is the result of a thrombotic complication of coronary artery disease or some other condition. Examined from this perspective, one might consider cardiac troponins to be plagued by “false positive” results. If the clinician examines elevated cardiac troponins as a marker of myocardial injury, the “false positive rate” declines substantially. Careful consideration of the clinical circumstances and the science of diagnostic testing will improve the practical utility of these laboratory studies.


54. Colombo A, Stankovis G. Nothing is lower than 0, and 3 is closer to 0 than to 5- medicine is not arithmetic. Eur Heart J 2002;23:840-2.


