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Troponin Elevation in Critically Ill Patients

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Abstract

A common problem in the intensive care unit is interpreting elevated cardiac biomarkers in patients hospitalized for serious non-cardiac diseases. The following case example demonstrates the importance of the clinical context when interpreting the cardiac biomarkers in critically ill patients. Elevated cTn in critically ill patient should be investigated thoroughly and distinction between Type1 myocardial infarction from Type 2 is established. There are numerous causes of troponin release due to myocardial damage, while some are related to myocardial ischemia others are not. Discrimination of Type 2 MI from Type 1 MI and troponin release due to non-coronary diseases is challenging. However, discrimination is paramount in order to provide timely and appropriate treatment.

Case

Mr C is a 55 year old male without history of coronary artery disease (CAD) and good exercise tolerance with METS of 7-10. Family history of CAD is the only risk factor in his history. The patient underwent an extensive abdominal and pelvic surgery for urinary bladder cancer. The intraoperative course involved massive transfusion but there was no hypotension, and pressors were not needed. Postoperatively he was left intubated on mechanical ventilation and aggressive resuscitaion continued in the ICU. Patient was extubated after 24 hours. On postoperative day 2 he developed sinus tachycardia, heart rate 130-150, without hypotension or desaturation. Cardiac troponins were elevated. Work up for pulmonary embolism was negative. Transthoracic echocardiography showed no wall motion abnormality. Cardiologist diagnosed him with 'troponin leak' without need for further cardiac workup.

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consists of 3 subunits, troponin T, troponin I, and troponin C.

Specificity for cardiac isoforms is the basis for the clinical utility of troponin T and troponin I assays. Troponin C is not used clinically because both cardiac and smooth muscle share troponin C isoforms.

Troponin elevations are indicative of myocardial injury in patients who are critically ill, especially patients with systemic inflammatory response syndrome (SIRS) and sepsis, and are associated with worse prognosis. In a recent study Elevated cTnI was an independent prognosticator of mortality (odds ratio, 2.020; 95% confidence interval, 1.153-3.541) after adjusting for other significant variables.

Also, Vasile et al. [24] found that in patients admitted to the ICU for respiratory disorders, cTnT elevations are independently associated with in-hospital, short-term and long-term mortality.

Apart from ischaemia, several factors may contribute to microinjury and minimal myocardial cell damage in setting of septic shock. A possible direct cardiac injury and myocytotoxic effect of endotoxins, cytokines, or reactive oxygen radicals induced by infectious process and produced by activated neutrophils, macrophages, and endothelial cells have been postulated. Serum troponin elevations are not necessarily due to an acute coronary syndrome (ASC). A variety of conditions in the ICU, such as sepsis, hypovolemia, atrial fibrillation, heart failure, pulmonary embolism, myocarditis, pericarditis, myocardial contusion, acute right heart overload, trauma as occurs during cardiopulmonary resuscitation, electrical cardioversion and renal failure can lead to serum troponin elevations. Therefore, troponin release and elevation by itself is not enough to establish diagnosis of ACS.

In one series of 21 patients with elevated troponin levels and a normal coronary angiogram, the following etiologies for troponin elevations were suggested [5]

Tachycardia - 28 percent

Pericarditis - 10 percent

Heart failure - 5 percent

Strenuous exercise - 10 percent

No clear precipitating event - 47 percent

When the pretest probability for the diagnosis of CAD is low, serum troponin level becomes less valuable for the diagnosis of ACS and may lead to unnecessary cardiac evaluation or even divert attention from the true underlying clinical problem.

Troponin can be elevated in:

1) Prolonged ischemia, in which myocytes are irreversibly damaged. The cell membrane degrades, followed by the gradual release of cytosolic complexes.

2) Conditions that produce increased myocyte membrane permeability.

3) Myocardial depressive factors released in the setting of sepsis cause degradation of free troponin to lower-molecular-weight fragments.

4) Wall stress may lead to ventricular microinjury and microinfarction. Direct proof of these phenomena is lacking and it is highly controversial.

While in the first condition myocardial necrosis occurs, in the last 3 it does not.

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The 2007 Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation (ESC/ACCF/AHA/WHF) Task Force for the definition of myocardial infarction refers to a Type 2 MI when the event is secondary to ischemia due to either an increased oxygen demand or a decreased supply in the absence of a primary coronary event.

Type 1: MI consequent to a pathologic process in the wall of the coronary artery (e.g. plaque erosion/rupture, fissuring, or dissection)

Type 2: MI consequent to increased oxygen demand or decreased supply (e.g. coronary artery spasm, coronary artery embolus, anemia, arrhythmias, hypertension or hypotension)

Type 3: Sudden unexpected cardiac death before blood samples for biomarkers could be drawn or before their appearance in the blood

Type 4a: MI associated with percutaneous coronary intervention

Type 4b: MI associated with stent thrombosis

Type 5: MI associated with coronary artery bypass graft surgery

The ESC/ACCF/AHA/WHF task force for the definition of MI agreed on the following definition of MI;

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) above the 99th percentile of the upper reference limit together with evidence of ischaemia with at least one of the following: Ischaemic symptoms, electrocardiography (ECG) changes of new ischaemia, development of pathologic Q-waves in the ECG or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Earlier symptoms and routine ECG surveillance in critically ill patient can not be relied upon. Because very minor damages on the heart muscle can be detected with the new high-sensitivity troponin methods, elevated cTn levels indicate cardiac injury, but do not define the cause of the injury.

Myocardial oxygen demand and serum troponins are increased in a number of clinical settings: sepsis, septic shock, the systemic inflammatory response syndrome (SIRS), hypotension, hypovolemia and atrial fibrillation or other tachydysrhythmias.

In these settings, increased myocardial oxygen demand can be due to:

Tachycardia

Cardiac volume or pressure overload.

Increases in cardiac output to accommodate increased systemic oxygen consumption

Simultaneously, myocardial oxygen delivery may be reduced due to the following:

Reduced coronary perfusion, due to both tachycardia, which reduces diastolic time, and reduced perfusion pressure in the setting of hypotension and increased cardiac filling pressures.

Decreased oxygen delivery to the heart.

A 2006 review evaluated 20 observational studies involving 3278 critically ill patients in which cardiac troponin concentrations were reported. The following findings were noted [7]. The frequency of elevated cardiac troponin was 12 to 85 percent, with a median of 43 percent. In six studies in which adjusted analyses were performed, elevated cardiac troponin was associated with a significantly increased risk of death (OR, 2.5; 95 percent CI, 1.9 to 3.4). It is not always possible to use symptoms as a major guide to diagnose ACS in patients who are intubated or sedated. ECG changes can be transient and be missed especially in the presence of baseline abnormalities such as a paced ventricular rhythm, left bundle branch block, or pre-existing ST–T abnormalities.

Routine ICU ECG surveillance has a low sensitivity (3%; 95% CI, 2–3%) for detecting ECG evidence suggestive of prolonged myocardial ischemia compared with frequent 12-lead ECGs. Also, the majority of ischemia occurred in leads V2, V3, and V4, suggesting that the routine practice of monitoring leads II and V5 may not be optimal. Rennyson et al. [20] showed that the routine screening for myocardial ischemia in the ICU setting remains difficult. ST-segment elevations that are detected periodically or when myocardial ischemia is clinically suspected yield an extremely low sensitivity and specificity for diagnosing acute myocardial infarction.

ICU patients with severe non-cardiac problems often have relative contra-indications to anticoagulants, or cardiac catheterization and intervention. Non-invasive evaluation can also be limited in such patients of major concern is the possibility that both can be occurring at the same time, with the stresses in critically ill patient causing acute progression of coronary lesions (TYPE 1) concomitant with cell damage from hypoxia or hypo-perfusion of non-coronary etiology (TYPE 2). The diagnosis of TYPE 2 MI is advantageous not only in the management of patients but also to assist in quality review and improvement. Criteria for optimal care of ACS often include time to intervention (Door to balloon time). But this measure is not applicable in patients such as the one presented here (Non-ischemic myocardial injury). Using an alternative diagnosis will help in avoiding misclassification.

When making the diagnosis of TYPE 2 MI, the extreme sensitivity of troponin for detecting myocardial injury/infarction makes it imperative to place all results in clinical perspective. In fact transient troponin elevations can be detected in athletes at the end of a marathon, with no evident functional consequences [14]. Elevated troponin values can identify critically ill patients with a worse prognosis, as in vascular surgery patients who have perioperative troponin elevations [15]. Chronic, low-level elevations in troponin have been documented in stable patients with renal failure, heart failure, left ventricular hypertrophy, and diabetes mellitus, and the list is growing.

It is important to differentiate a new coronary event from a non-coronary source of myocardial damage. TYPE 2 MI is not specific to non-coronary myocardial injury, because it also includes myocardial infarction caused by coronary spasm or embolism and both are coronary events. Hence a new descriptive term is needed for a non-coronary source of myocardial injury. We think that non-coronary troponin elevation deserves a separate diagnostic subcategory if not a category by itself. Tachycardia alone has been implicated as a cause of troponin elevations in small case series. In one series of 21 patients with elevated troponin I levels and normal coronary angiograms, tachycardia was determined to be the explanation of the troponin elevation in six patients [8]. A second series described four patients with troponin elevations after episodes of supraventricular tachycardia (SVT), who had no evidence of CAD.

Finally, ver Elst et al. [22] did not find evidence of irreversible myocyte necrosis in autopsy cases of septic shock where there was a positive premortem cTn. These authors suggested the possibility of cTn release as reversible injury in these patients.

As for our patient: with further resuscitation his tachycardia resolved and he was discharged to the floor. After normalization of troponin levels, transthoracic echocardiography showed no regional wall motion abnormality or new valvular lesions. He was then discharged from the hospital, and instructed to follow up with his cardiologist. Stress test as an outpatient was negative.

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