ELEVATED TROPONIN IN THE ABSENCE OF MYOCARDIAL INFARCTION

LIONEL J. MALEBRANCHE, MD, RPVI, FACC
INVASIVE CARDIOLOGIST UPH
REGIONAL PHYSICIAN COUNCIL
PHYSICIAN GOVERNANCE COUNCIL

ALEXA MILLER, MD
FAMILY MEDICINE RESIDENT UIC

I HAVE NO RELEVANT FINANCIAL DISCLOSURES

- Objectives
- Definition
- Cellular mechanisms
- Demand ischemia
- Troponin elevation in ischemic heart disease
- Non MI related troponin elevation
- Case review

Definition

- Cardiac troponin is the standard test to confirm acute MI
- Troponin complex has 3 sub units: Troponin T, I and C
- Cardiac troponin are regulatory proteins that control calcium mediated interaction of actin and myosin
- Assay in use specific for the myocardium
- Not specific for acute thrombotic occlusion of coronary artery
- Increased troponin seen in sepsis, fib, HF, PE, myocarditis, myocardial contusion, renal failure, etc.
- False positive due to skeletal muscle injury is rare

PATHOPHYSIOLOGY

- prolonged ischemia—>myocardial necrosis—>gradual release of myofibril-bound cytosolic complexes—> cardiac troponin release
- increased myocyte permeability
- myocardial depressive factors seen in sepsis and other inflammatory states—> degradation of free troponin to lower weight fragments.
- Troponin may be elevated without myocyte cell death
- Myocardial depression during sepsis is fully reversible

4TH UNIVERSAL DEFINITION OF MI

1. The criteria for **type 1 MI** includes detection of a rise and/or fall of cTn with at least one value above the 99th percentile and with at least one of the following:
    a. Symptoms of acute myocardial ischemia;
    b. New ischemic electrocardiographic (ECG) changes;
    c. Development of pathological Q waves;
    d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
    e. Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

2. The criteria for **type 2 MI** includes detection of a rise and/or fall of cTn with at least one value above the 99th percentile and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
    a. Symptoms of acute myocardial ischemia;
    b. New ischemic ECG changes;
    c. Development of pathological Q waves;
    d. Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

4TH UNIVERSAL DEFINITION OF MI

3. Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (>99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% of the baseline value when it is above the 99th percentile, but it is stable or falling.

4. Coronary intervention-related MI is arbitrarily defined by elevation of cTn values **>5** times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:
   a. New ischemic ECG changes;
   b. Development of new pathological Q waves;
   c. Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow or distal embolization.

PATHOPHYSIOLOGY

- Demand ischemia
  - Mismatch between myocardial oxygen demand and supply
  - evidence of ischemia w/o CAD
  - 2018 Universal definition of MI (ESC/ACC/AHA) refers to type 2 MI when increased oxygen demand or decreased supply in absence of primary thrombotic process.
  - May be seen in sepsis, septic shock, SIRS, Hypotension, hypovolemia, atrial fibrillation and other tachyarrhythmias

PATHOPHYSIOLOGY

- Decreased oxygen supply due to:
  - tachycardia: decreased diastolic time with reduction of coronary perfusion
  - hypotension with reduced perfusion pressure
  - decreased oxygen delivery to myocardium

PATHOPHYSIOLOGY

- Direct effect related to cathecolamines and tissue necrosis factor

“Elevated value of cardiac troponin in absence of clinical evidence of ischemia should prompt a search for other causes of myocardial necrosis.”

–Universal definition of Myocardial infarction

ELEVATION IN GENERAL POPULATION

- Most individuals have small amounts of measurable (hs cTn) in their blood
- precise mechanism of release not established
- detectable values with a hs assay should not be considered abnormal
- Higher values indicate greater risk whether they have known CVD or not
- some individuals with known structural heart disease may have chronic stable elevations above 99th percentile in absence of ACS
- ACS can be assessed if significant change over serial measurements

Causes of elevated troponin

Myocardial ischemia
Acute coronary syndrome
STEMI
NSTEMI
Other coronary ischemia
Arrhythmia: tachy- or brady-
Cocaine/methamphetamine use
Coronary intervention (PCI or cardiothoracic surgery)
Coronary artery spasm (variant angina)
Stable coronary atherosclerotic disease in setting of increased O^2 demand (eg, tachycardia)
Severe hypertension
Coronary embolus
Aortic dissection
Coronary artery vasculitis (SLE, Kawasaki)
Non-coronary ischemia
Shock (hypotension)
Hypoxia
Hypoperfusion
Pulmonary embolism
Global ischemia
CT surgery
Myocardial injury with no ischemia
Comorbidities
Renal failure
Sepsis
Infiltrative diseases
Acute respiratory failure
Stroke
Subarachnoid hemorrhage
Specific identifiable precipitants
Extreme exertion
Cardiac contusion
Burns >30% BSA
Cardiotoxic meds: anthracyclines, herceptin
Electrical shock
Carbon monoxide exposure
Other
Apical ballooning (Takotsubo)
Myocarditis
Myopericarditis
Rhabdomyolysis involving cardiac muscle
Hypertrophic cardiomyopathy
Peripartum cardiomyopathy
Heart failure, malignancy, stress cardiomyopathy

BSA: body surface area; CT: cardiothoracic; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; SLE: systemic lupus erythematosus; STEMI: ST elevation myocardial infarction.

WHAT EVIDENCE DO WE HAVE?

CAUSES OF ELEVATED TROPONIN I WITH A NORMAL CORONARY ANGIOGRAM

- 21 patients with elevated trop and normal coronary angiogram
  - 28% due to tachycardia
  - 10% pericarditis
  - 5% heart failure
  - 10% strenuous exercise
  - 47% no clear precipitating event

ELEVATED CARDIAC TROPONIN CONCENTRATION IN THE ABSENCE OF AN ACUTE CORONARY SYNDROME

- 20 patients treated in ICU
- 85% had troponin I elevation
- 10/17 had no significant CAD
- 5 with elevated cTnI died, all had autopsies. Coronary arteries were normal in 4/5

TROPONIN AS A RISK FACTOR FOR MORTALITY IN CRITICALLY ILL PATIENTS WITHOUT ACS. JACC 2003

- 58 patients admitted to ICU for sepsis, septic shock or SIRS
- 32 had elevated troponin
- mortality higher in patients with troponin elevation (22% vs 5%)
- TNF, IL6 and CRP significantly elevated in patients with elevated troponin
- CAD excluded in 72% of troponin positive patients

KEY POINTS

- Troponin elevation is common in sepsis
- Affected patients often have no significant CAD
- Worse prognosis in these patients
- Unclear if cardiovascular intervention would improve outcome
- Elevated troponin does not equate acute MI

WHY IS IT IMPORTANT TO IDENTIFY THE ETIOLOGY OF TROPONIN ELEVATION?

CASE 1

- 69 yo male with PMHx of prostate cancer, recent RUE DVT on Eliquis, OSA, recent diagnosis of invasive lung cancer
- Methodist admission 2 weeks prior: Presented with chest pain and elevated troponin 0.28. Had cardiac cath with clean coronaries.
- OSF admission 2 days later: Presented with aphasia, found to have left frontal convexity SAH as well as multiple likely embolic left sided infarcts. Not a candidate for tPA. Anticoagulation held due to SAH. No neurosurgical intervention.
- Presented to the Methodist ED with new aphasia, repetitive right hand movements

CASE 1

- VS: BP 144/83, P 70, RR 18, SpO2 97% on room air
- Patient with expressive aphasia on exam but following commands, mild right-sided weakness and hyperreflexia
- Labs remarkable for WBC 12.3, troponin 1.7
- CT head: Subacute infarct in the left parietal lobe (previously seen on recent admission)
- Neurology consulted, started heparin gtt
- MRI brain: Multiple new acute infarcts in left frontal and parietal lobes
- TEE performed demonstrated large thrombi attached to mitral valve

WHAT IS THE DIFFERENTIAL FOR TROPONIN ELEVATION IN THIS CASE?

ACUTE CVA

- Both cTn levels and ischemic ECG changes described in acute CVA or ICH
- One series of 149 patients with acute stroke
- 27% had elevated troponin I
- Elevated troponin I noted in 2 case series with SAH
- troponin elevation correlated with severity of neurologic injury and CV abnormalities
- It predicts higher mortality

ELEVATED TROPONIN T AFTER ACUTE ISCHEMIC STROKE

- 114 consecutive ischemic stroke patients confirmed by MRI
- Troponin T measured on admission
- ECG performed and stroke severity assessed with NIHSS

ELEVATED TROPONIN T AFTER ACUTE ISCHEMIC STROKE

- Troponin T elevated in 20 (17.6%)
- patients had higher age, elevated creatinine and ischemic ECG changes
- troponin was higher with more severe stroke
- No association between troponin and location of stroke and afib in this study

HYPOTHESIS

- Hypothesis that damage to centers regulating autonomic function can cause autonomic dysregulation—>sympathetic overflow or neurogenic myocardial injury
- Some studies have shown troponin level was higher in right insular, brainstem or MCA strokes
- Silent acute MI before stroke

EARLY ELEVATED TROPONIN LEVELS AFTER ISCHEMIC STROKE SUGGEST CARDIOEMBOLIC SOURCE

- 1234 patients with Acute ischemic stroke
- 1129 had admission troponin
- 10% had elevated troponin (113/1129)
- adjusted models found association between troponin positivity and embolic stroke (OR 4.46; 95% CI)
- cardioembolic stroke (OR, 5; 95% CI)

ACUTE CVA MECHANISM OF ELEVATED TROPONIN

- Imbalance of autonomic nervous system with excess sympathetic activity and increased catecholamine effect on myocardial cells.
- Similar mechanism described in stress induced cardiomyopathy

CKD AND TROPONIN ELEVATION

- Stably elevated troponin commonly observed in CKD with no myocardial damage
- Decreased clearance vs increased cardiac release (favored theory) not known
- Cause of low level troponin elevation is likely chronic myocardial injury but not the result of CAD

CKD AND TROPONIN ELEVATION

- A change in troponin concentration (rise and fall over 3-6 hours) should be used to define MI
- Either troponin T or I may be used with serial assessment
- Greater than 20% change in serially measured troponin is an acceptable threshold change for AMI diagnosis
- Clinical assessment favored over laboratory review

CASE 2

- 63 yo African American male with PMHx of seizure disorder, HTN, EtOH abuse, ICH s/p VP shunt
- Brought to the ED by EMS after a seizure after not taking Keppra for 2-4 days
- Patient postictal, provides limited history, disoriented to place and time in the ED
- VS: BP 143/76, P 58, RR 18, T 98.7, SpO2 98% on room air
- WBC 11.5, electrolytes WNL, creatinine at baseline. EtOH neg. DAU + benzos, opiates, THC. Keppra level <2
- CT head: Old ischemic changes, no acute process. VP shunt in place, no midline shift. CT C spine unremarkable
- CXR: No acute cardiopulmonary process
- EKG: Early repolarization pattern with mild diffuse upsloping ST changes
- Neurology consulted; patient given loading dose of Keppra IV, then previously effective home dose resumed
- Patient admitted for observation

CASE 2

- The following morning, the patient's EKG was repeated after the initial EKG was reviewed by the primary team and there was concern for ST changes. Repeat was unchanged from initial. Troponin was obtained due to ST changes and was elevated at 0.142; patient asymptomatic. Cardiology consulted.
- TTE: No regional wall motion abnormalities, normal systolic and diastolic function
- Patient discharged on hospital day 2 with recommendation of cardiology followup for elective assessment of ischemic risk
- Outpatient Lexiscan: Normal, no evidence of ischemia

CARDIAC TROPONIN I ELEVATION AFTER EPILEPTIC SEIZURE

BACKGROUND:

Cardiac troponin-I (cTNI) is highly specific biomarker to prove myocardial damage, e.g. in acute coronary syndrome (ACS). However, it occurs in other conditions as well. We therefore analysed cTNI increase in patients after generalized convulsive seizure.

METHODS:

Consecutive patients admitted with acute generalized convulsive seizure were included in case of cTNI measurement on admission. Among 898 selected cases, 53 patients were referred secondary to our department; in 845 cases cTNI measurements on admission were available. In case of multiple admissions (81 cases), only the first admission entered our analysis. In 17 patients elevated cTNI was determined due to ACS; in one patient a myocarditis was found. 5 patients suffered of relevant renal insufficiency. Finally 741 patients were included in the analysis. A cTNI cut-off level of ≥ 0.1 ng/ml was considered. Factors associated with a cTNI increase were analysed subsequently.

RESULTS:

The mean age of the study population (n = 741) was 47.8 years (SD ± 18.6), 40.9% were female. In 50 patients (6.7%) a cTNI elevation of unknown origin was found; no obvious cardiac involvement could be detected in these patients who all remained asymptomatic. A vascular risk profile (including at least hypertension, hypercholesterolemia or diabetes) (OR = 3.62; CI: 1.59 to 8.21; p = 0.001) and elevated creatine kinase on admission (OR = 2.36; CI: 1.26 to 4.39; p = 0.002) were independent factors associated with cTNI release.

CONCLUSION:

cTNI release occurs in patients with generalized convulsive seizure with predominance in patients with vascular risk profile.

SEIZURE AND ELEVATED TROPONIN

- Elevated troponin after GTC seizure related to demand ischemia
- increased muscular activity
- massive catecholamine release from sympathetic nerve endings
- increased heart rate, arterial blood pressure and myocardial contractility
- considered a physiological stress test

CASE 3

- 54 yo African American female with PMHx of HTN, DMII, HLD, hypothyroidism, OSA, migraines
- Presented to the ED with episode of sharp chest pain, diaphoresis, and lightheadedness
- In SVT in ED with rate in 170s, converted to NSR with vagal maneuvers
- VS: BP 146/84, P 95, RR 18, O2 97% on room air
- WBC 15.2, alk phos 145, AST 135, ALT 138, lactic acid 3.9. VBG unremarkable
- CXR: Opacity in left lung base
- EKG after conversion to NSR: T wave inversion in anteroseptal and inferior leads
- Found to have sepsis secondary to UTI, treated with rocephin. Lactic acidosis improved with IVF. Admitted to hospitalist service.

CASE 3

- Hospital day 2: Patient reported chest pressure and SOB. EKG unchanged from prior. Troponin elevated at 45.7, pro-BNP 1295.
- Cardiology consulted. Started on heparin gtt, nitro paste, metoprolol, transferred to cardiac unit.
- TTE: Evidence of hypertrophic cardiomyopathy with severe apical asymmetric hypertrophy. EF 70%. Diastolic dysfunction, small pericardial effusion. Patient given one dose of IV Lasix
- Cardiac cath performed and showed no CAD
- Further HPI: Chest pain pleuritic, worse when lying flat, improved with sitting up. Concern for myopericarditis. CRP elevated at 1.7. Cardiac MRI ordered.
- Cardiac MRI: No evidence of myocarditis, redemonstration of HOCM

WHAT IS THE DIFFERENTIAL FOR THIS PATIENT?

MYOCARDITIS

- Troponin release in myocarditis results from increased permeability of cardiomyocyte cell membrane
- not reflectively exclusively of cell necrosis
- persistent elevation of cardiac enzymes indicative of ongoing necrosis

ELEVATED TROPONIN IN HEART FAILURE

- troponin elevation tends an adverse prognosis
- 2 mechanisms:
  - myocardial strain (related to volume and pressure overload—> excessive wall tension —> myofibrillar damage)
  - myocyte death

PATHOPHYSIOLOGY IN HEART FAILURE

- Close correlation between troponin levels and BNP
- Troponin degradation demonstrated with increased preload independent of myocardial ischemia in isolated rat hearts
- Myocardial wall stress—>decreased subendocardial perfusion—>trop elevation and LV dysfunction

HEART FAILURE AND MYOCYTE DEATH

- in vitro experiment with myocytes established links between myocardial wall stretch and programmed cell death
- progressive myocyte loss plays role in progressive cardiac dysfunction
- Activation of RAS; sympathetic stimulation, inflammatory mediators and integrin stimulation

KEY POINTS

- cardiac troponin is highly sensitive biomarker of myocardial cell damage (injury) but not always due to ischemic heart disease
- highly specific for myocardial cell release but not for ACS
- increased levels can be seen in variety of non thrombotic diseases
- can be seen in myocardial ischemia—> type 2 MI
- confers a worse prognosis across the spectrum
- routine assessment is not justified