

Title: Evaluating the Role of Cardiac Enzymes in the Diagnosis of AMI

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Date: July 26, 2010

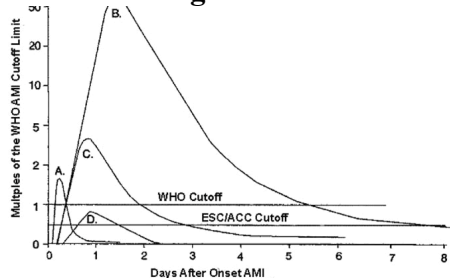
PICO:

- P: In patients presenting to the ED with complaints of chest pain
- I: Can the use of “delta” cardiac enzymes over a shorter time period
- C: Compared with traditional serial markers at arrival and subsequent set 6 hours later
- O: Expedite a patient’s workup to rule in/out AMI?

Clinical Scenario:

A 45 year old male presents to the ED with complaints of left sided chest pain. He reports that it is a pressure sensation without radiation. He reports that the pain started acutely 4 hours prior and has been persistent over this time. No prior history of cardiac disease, hypertension, or other cardiac risk factors. Can serial cardiac enzymes expedite his ED course and can they change his disposition?

Clinical background:



Timing of release of common cardiac markers of necrosis. Peaks A, B, and C respectively demonstrate release of myoglobin, troponin, and CK-MB in acute myocardial infarction as defined by WHO diagnostic criteria. Peak D demonstrates troponin release in troponin positive/CK-MB negative acute coronary syndrome now defined as acute myocardial infarction by ESC/ACC diagnostic criteria¹.

ESC/ACC Diagnostic Criteria for Acute Myocardial Infarction (One of following criteria)²:

1. Typical rise and gradual fall (troponin*) or more rapid rise and fall (CK-MB*) of biochemical markers of myocardial necrosis with at least one of the following:
 - a. ischemic symptoms;
 - b. development of pathologic Q waves on the ECG;
 - c. ECG changes indicative of ischemia; or
 - d. coronary artery intervention.
2. Pathological findings of acute myocardial infarction.

*An increased value for cardiac troponin or CK-MB should be defined as a value that exceeds the 99th percentile in a reference control group. In most situations, elevated values for biomarkers should be recorded from two successive blood samples to diagnose MI. Cardiac troponins are the preferred biomarker for myocardial damage

“By virtue of these kinetics, the temporal rise of the serum concentration of CK-MB and cardiac troponin typically does not permit detection of myocardial necrosis very early (1–3 h) and does not support maximal sensitivity of these markers until 6 or more hours after the onset of MI.”⁴

Search Outcome:

Authors, Date, and Country	Study populations	Study Type (Level of evidence)	Outcomes	Key Results	Study Limitations
Hamm CW, et al 1997 Germany	773 consecutive patients w/ chest pain < 12 hours w/o ST-segment elevation on EKG	Prospective observational Treating physicians blinded to cTnI (not cTnT)	Comparison of bedside cTnT vs cTnI assays Samples drawn at baseline and at least 4 hours for 2 sets > 6hr apart total	6% incidence of AMI 44/47 AMI + w/ cTnT vs 47/47 + w/ cTnI 126 had + cTnT vs 171 + for cTnI 1.1% w/ - cTnT had AO at 30 d vs 0.3% cTnI (therefore NPV= 98.9 & 99.7, respectively)	Small sample size

Fesmire FM, et al 2001 USA	125 consecutive pt's presenting to ED w/ possible ACS	Prospective Observational	Baseline and 2 hour Δ CK-MB and cTnI 30 day outcomes (comparing above) with ROC Compare Axsym devise vs Stratus CS Rise in Δ cTnI = \geq +0.02 in 2-hr suggestive of AMI	5.8% incidence of AMI \uparrow ROC for Δ cTnI c/w CK-MB (0.69 \pm 0.07 vs 0.81 \pm 0.06) Δ cTnI= 61.9% sens (38.4-81.8) for 30 day AO + Δ = 31 x \uparrow OR for 30 day AO (p<0.0001; 95% CI 9-108) No changes in specificity across all 4 modalities	Small sample size Low % of AMI in study population Better for r/in vs r/o
NG, SM, et al 2001 CA, USA	1,285 consecutive pt's to ED with c/o possible ACS	Prospective Cohort	Evaluation of diagnosis/dispo w/in 90 minutes Serial CE's at 30, 60 & 90 min 1/5 clinical pathways (see appendix A)	AMI diagnosed w/in 90 minutes (Sens-100%, spec-94%) R/O AMI w/ - CE's at 6 hours (100% sens) \downarrow >40% CCU admissions 99% d/c'ed home w/in 90 min. and negative w/u (1 missed AMI)	Limited population (VA patients) ? applicability No CI reported
MacRae AR, et al 2006 ON, Canada	258 ED pt's w/ symptoms of possible cardiac ischemia	Retrospective study using stored samples (1996) Samples were drawn at presentation \rightarrow hourly until \geq 6hr after onset of Sx; 9, 12, 24, 48 hr's	Evaluation of Δ cTnI at hour increment intervals s/p onset of Sx Minimal Time to detect + cTnI from time of onset for AMI Used cutoff of 20% Δ , if not initially +	No statistically significant change in detection of AMI for Δ 3 hr vs \geq 4hr, \geq 5hr, \geq 6hr (36.4%, 34.5%, 33.7%, 35.7% prevalence respectively) (P>0.05) Diagnosis of AMI would have been made earlier (avg 3.5 hr) if cTnI draw 6hr from onset in 83% of pt's Unchanged detection of AMI if 1 sample drawn \geq 6hr from onset	Retrospective Stored samples Funded by Beckman Coulter, Inc (maker of assay)

Apple FS, et al 2009 MN, USA	381 pt's w/ ED presentations of possible ACS	Prospective Observational, Blinded	cTnI on admission and 6 hours later Sensitivity & Specificity of Δ cTnI > 10%, 20% & 30% via ROC curve Cardiac Event or Death at 60 days using Cox proportional hazard regression	52 AMI (13.6%) Sens/Spec of initial= 69.2% & 77.5% Repeat \uparrow to 94.2% & 81.2% (P=0.99) \uparrow AuROC 0.82 (95%CI 0.77-0.85) \rightarrow 0.96 (95%CI 0.94-0.98) No statistically sig change for Δ of 10% or 20%; optimal cutoff via ROC of $\delta > 30\%$; unchanged sensitivity, but \uparrow specificity (to r/o AMI)	Under powered (P=0.99) Study limited to VITROS Troponin I ES End points of AMI (not ACS/UA) and prognostic adverse events, not disposition
Keller T, et al 2009 Germany	Multicenter study 1818 consecutive pt's w/possible ACS	Prospective observational Final diagnosis made by 2 separate cardiologists, blinded to results of cTnI	Sensitivity/Specificity of biomarkers at admission, 3 hr & 6hr Raise or fall in cTnI > 30% w/in 3-6 hrs after admission	22.7% incidence of AMI Sens= 88% > 6hr after onset of CP, 95% 6-12 hrs, & 100% for > 12 hrs Specif unchanged at each time (93%) 100% detection w/ Δ w/ draw @ 3hr for AMI and Δ @6 hr (regardless of onset time) Highest accuracy for Trop I using AUC ROC c/w other biomarkers (esp w/in 3hr of Sx onset)	AMI \neq UA Focus on ROC for each biomarker

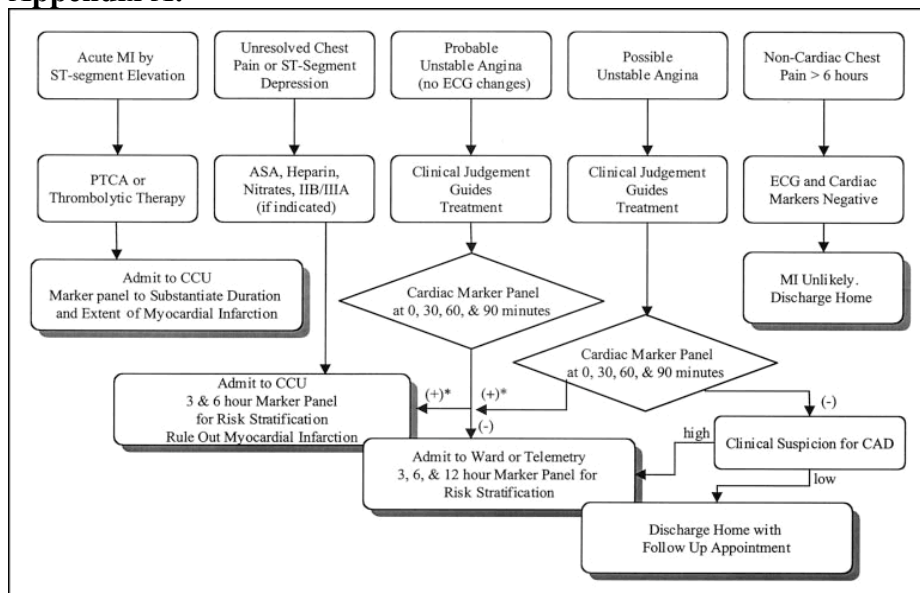
Comments:

1. Is the intent to rule in vs rule out AMI in ED patients? Is the goal to diagnosis AMI vs UA?
2. Does this change usage of "chest pain observation" and "ED stress testing?"
3. The time of onset of symptoms should be incorporated in the use of serial cardiac enzymes, with admission to ED as "time zero" only in unknown exact time of onset.

Clinical bottom line:

A single cardiac enzyme ≥ 6 hours from presentation has good positive & negative predictive values for AMI and serial cardiac enzymes (highly sensitive cTnI, in particular) and Δ levels are useful for ruling in or out AMI w/ > 30% change at 3 hours (vs. traditional 6 hours).

Appendix A:



Appendix B (ACEP Clinical Policy Statement)²:

Is there a preferred regimen of serum marker testing in the ED for the exclusion of non-ST-segment elevation AMI?

Inclusion Criteria. Patients with symptoms suggestive of acute coronary syndromes presenting less than or equal to 12 hours of symptom onset.

Patient Management Recommendations

Level A recommendations. Do not utilize cardiac serum marker tests to exclude non-AMI acute coronary syndromes (ie, unstable angina).

Level B recommendations. Utilize any of the following cardiac serum marker tests to exclude non-ST-segment elevation AMI as defined by the World Health Organization (WHO) or modified WHO criteria (Figure 1):*

1. A single negative CK-MB mass, Troponin I, or Troponin T measured 8 to 12[†] hours after symptom onset.‡
2. A negative myoglobin in conjunction with a negative CKMB mass, or negative Troponin§ when measured at baseline and 90 minutes in patients presenting less than 8 hours after symptom onset.‡
3. A negative 2-hour delta_ CK-MB mass in conjunction with a negative 2-hour delta_ Troponin§ in patients presenting less than 8 hours after symptom onset.‡

Level C recommendations. None specified.

*There is insufficient evidence at this time to make any recommendations in regards to utilization of cardiac serum markers to exclude non-ST-segment elevation AMI using current Joint European Society of Cardiology(ESC)/ACC criteria for AMI (Figure 2).

†The exact timing of serum marker measurement as it relates to time of symptom onset should take into account the sensitivity, precision, and institutional norms of the assay being utilized, as well as the release kinetics of the marker being measured.

‡If time of symptom onset is unknown, unreliable, or more consistent with preinfarctional angina, then time of symptom onset should be referenced to the time of ED presentation.

§Only Troponin I has been investigated in the serial 90 minute multimarker protocol and the 2-hour delta protocol.

_The appropriate delta values for exclusion of AMI should take into account the sensitivity and precision of the assay utilized and confirmed by in-house studies. It is also important that delta serum marker levels are measured on the same instrument due to subtle variations in calibration among individual instruments of the same model.

Appendix C³:

Critical values to know about troponin assays

- *Lower limit of detection*: The lowest level detectable that differs from zero. Assays with a lower limit of detection are more sensitive.
- *Upper limit of normal*: Usually defined as the 95th percentile (mean \pm 2 standard deviations) in a presumably normal “reference” population. For troponin, the European Society of Cardiology / American College of Cardiology task force recommended that the 99th percentile (mean \pm approximately 3 standard deviations) be used as the cut-off point, above which any value should be considered abnormal.
- *Coefficient of variation (CV)*: A measure of how consistently an assay is able to produce the same result on the same sample. A CV of 10% is the level of precision suggested for troponin assays.
- *Receiver operating characteristic (ROC) curve*: The value at which the sensitivity of the troponin level is equivalent to that of the CK-MB level.

References:

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