2 hour troponin?

Scope of the problem

- Encounters attributable to symptoms of ACS:
  - 5-10% of all ED presentations
  - Up to 25% of hospital admissions

- Missed MI = high risk of MACE

- Need for safe discharge is a priority and a driver of physician behaviour

Risk stratification and decisions

- Cardiac troponins are the preferred biomarkers for myocardial infarction.

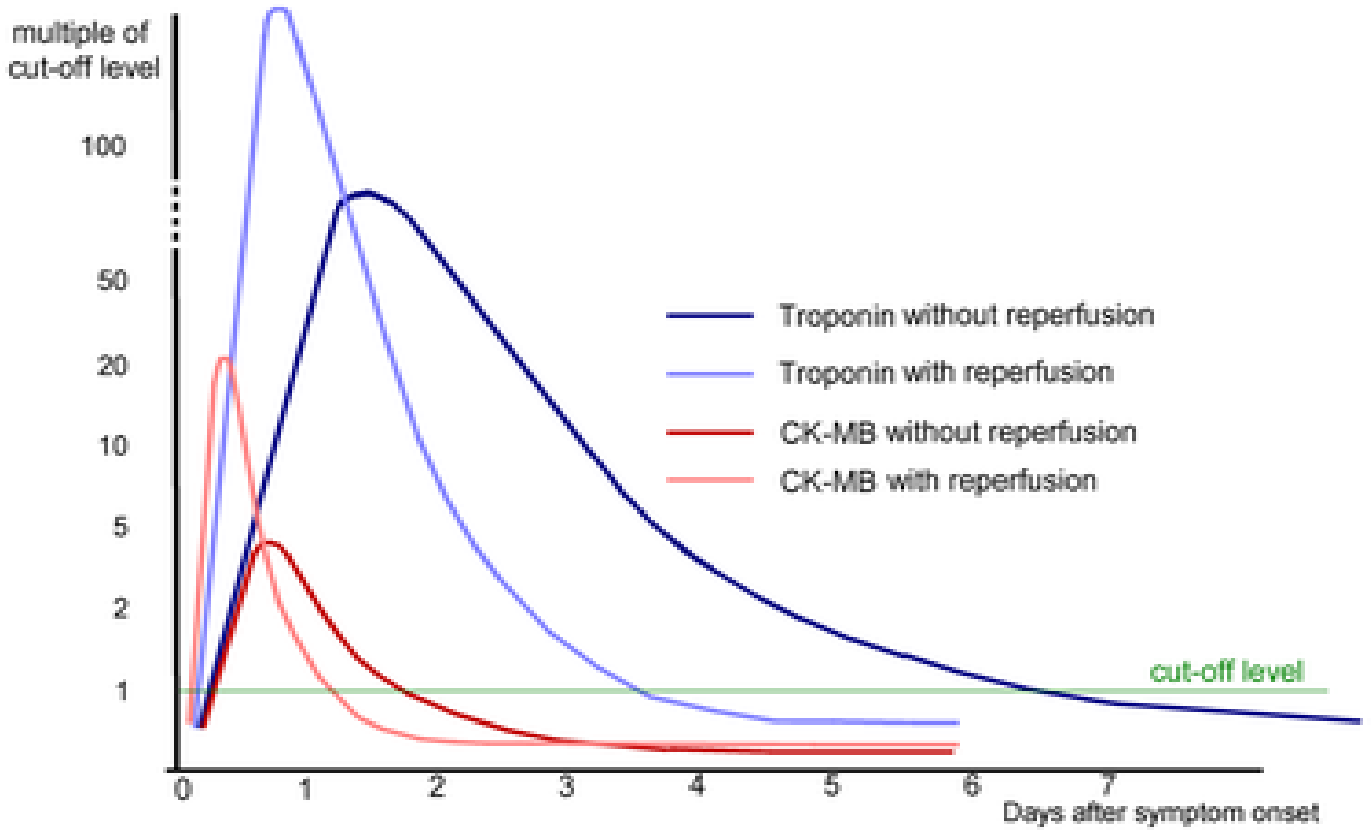
- When compared to patients with suspected ACS and normal troponin levels, patients with suspected ACS and elevated troponin levels have:
  - increased rates of MACE
  - more severe and complex coronary artery disease
    - Larger thrombus burden
    - Greater microvascular injury
  - Subsequently more favourable risk-benefit and cost-benefit ratios for interventions (meds/PCI)

What are we measuring?

- Troponin complex:
  - 3 protein subunits: T, I and C.
  - T and I are cardiac specific
    - T and I give the same information so choice of assay depends on equipment and vendor selection by central lab admin.
  - 95% of it is complexed with actin in myofibrils
  - About 5% is soluble in myocyte cytoplasm

- Ischaemia alters cell membrane integrity:
  - Initial release of cytoplasm pool
  - Then larger and more sustained release from contractile apparatus.
  - 4-6 hours for conventional troponin test.
  - May remain elevated for up to 2 weeks

Cardiac enzymes v. time



3rd universal definition of AMI

- Detection of increase, decrease, or both of cardiac biomarkers (pref troponin) with at least 1 value >99th percentile of upper reference limit

- And at least one of:
  - Symptoms of ischaemia
  - New significant ST-segment and T-wave changes or new LBBB
  - Development of pathological Q waves
  - Cardiac imaging consistent with iscahemia or infarction (e.g. new wall motion abnormality)
  - Angiography identifies a coronary artery thrombus.

Adapted from Thygesen et al. Circulation. 2012;126:2020-2035.

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Thygesen K et al. Circulation. 2012;126:2020-2035

Conventional assays

- A single trop level only has 70-85% sensitivity.
  - Therefore serials are necessary.

- Typical period of monitoring is 6-9 hours.

- Shorter intervals are appropriate among individuals with a low probability of MI who are also at low risk of MACE (major adverse coronary event) e.g death or ischaemic complications.
  - ADAPT trial. cTnI levels at 0 and 2 hours after arrival.

When do you take the levels?

- Serial samples
- First sample is taken at presentation.
- The interval between samples has to be >3h.
- At least one sample has to be taken >6h from the onset of symptoms.
  - Accuracy of patient recall is a concern, so many centers start the clock from time of ED presentation.
  - Most studies use presentation as 0hr.
- At Bendigo ED, 0hr is arrival time
  - If negative, repeated at 3h after arrival and at least >6h after symptom onset
  - If positive, repeated >6h

Delta troponin

- Universal definition of MI requires dynamic changes in troponin but does not guide us regarding the magnitude of change required.

- Relative troponin rise >50% from baseline

Multiple episodes of chest pain or late presentation

- Same testing protocol.
- A rising or falling pattern is not absolutely necessary to make the diagnosis of MI if a patient with a high pre-test risk of MI presents late after symptom onset
  - e.g. near the peak of the cTn time-concentration curve or on the slow-declining portion of that curve, when detecting a changing pattern can be problematic.

The specificity problem

- Troponins are specific for myocardial injury.

- However they are not specific for the mechanism of myocardial injury
  - Any condition that damages myocardiocytes can elevate troponin levels.

Acute causes of elevated troponin

ACUTE MI

- ACS (type 1 MI)
  - STEMI
  - NSTEMI
- Supply-demand mismatch (type 2 MI)
  - Severe HTN
  - Tachyarrythmia
  - Severe anaemia
- Decreased supply, non-ACS
  - Spasm
  - Embolism
- Drugs
  - Cocaine
  - Methamphetamines
- Procedure-related
  - PCI
  - CABG

NON-ISCHAEMIC MYOCARDIAL INJURY

- Direct myocardial damage
  - Congestive HF
  - Infection
    - Viral myocarditis
    - Endocarditis
  - Inflammation
  - Myocarditis
  - Pericarditis
  - Malignancy
  - Cancer chemotherapy
  - Traina
  - Electrical shock
  - Ablation procedures
  - Infiltrative diseases
  - Stress cardiomyopathy (Takotsubo)
- Other
  - PE
  - Sepsis
  - Renal failure
  - Stroke
  - Subarachnoid haemorrhage

Alcalai et al.

Arch Internal Med. 2007;167(3):276-281.

- Looked at all elevated trop levels in their hospital over a 1 year period.
- Only about half of elevated troponin levels were attributable to ACS (Alcalai et al.)
- In older patients with CKD, this decreased to 37%.
- But 2 year mortality of non-ACS group was more than 2x the ACS group, so not at all trivial.

What about high sensitivity Troponin?

PROs

- Increased sensitivity
- Higher NPV
- Lower false negative rate.

CONs

- Decreased specificity for MI
- Decreased PPV
- Higher false positive rate
- Gender-dependent values may be necessary.
- Relative troponin rises are common and more magnified and don't mean as much.

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- Higher sensitivity (82 vs 79%)
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- Gender-dependent values may be necessary.
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What about high sensitivity Troponin?

- A lowered specificity raises concerns about using these tests on populations with lower MI prevalence:
  - Probability of MI in typical chest pain observation unit is only 5%.
  - Based on recent population-based studies, 50% or more of patients in a typical chest pain observation unit would be expected to have a low but detectable troponin level with the highly sensitive assays.
- Problems in interpretation and management of non-ACS causes of troponin rise
- Increased downstream costs and risk of unnecessary tests.
- General increase in anxiety of everyone concerned.

There may be a future use for HsTn…

- Studies suggest that serial troponins may not be necessary among patients with undetectable HsTn levels
  - Except for those who present very early after symptom onset (<2 hours)

- May be also be useful in outpatient setting as a risk assessment tool.

What about Castlemaine ED?

- Point of care test = iSTAT cTnI (Abbott)
  - 0-99% Ref range of healthy pts is 0-0.08µg/L
  - Can detect trop levels from 0.02 to 50µg/L

- Follow up conventional cTnI sent by taxi to Healthscope Bendigo
  - Ref range 0 – 0.05µg/L
  - Turnaround time prolonged

iSTAT cTnI

- Whole blood passes over silicon chip with 2 types of antibodies to cTnI impregnated on it.
- 7 mins to create antibody-cTnI-antibody sandwich
- Then washed with a fluid substrate which is cleaved by antibody complex and leaves an electrochemically detectable product
- Product detected by sensor, electrochemical charge is proportional to cTnI conc of whole blood sample.

iSTAT technique

- Must place whole blood into cartridge within 1 minute of draw
- Otherwise, must put blood in sodium-heparin or lithium-heparin tube, invert tube 10 times, then use.
- No fingerprick samples
- No capillary samples

Issues with iSTAT

1. Accreditation / training required.
2. Storage and cold chain
   - Cartridges must be stored frozen
   - Once thawed, last 14 days
3. Maintenance, calibration and software updates.
4. Sample error
   - Haemolysed blood = decreased result
   - Partially-clotted blood = inflated result
   - Patient given immunoglobulins = theoretical
5. For ruling in MI at presentation (0 h), sensitivity 32%, specificity 92%. NPV > 90% and ROC AUCs > 0.90 after 6 h.
   - This is why a confirmation sample is required

Comparison

Characteristic	Contemporary cTnI	HsTnI	iSTAT cTnI
AUC	0.92	0.96	>0.9
99th % cutoff (µg/L)	0.05	0.0052	0.08
Sensitivity %	79	82	32
Specificity %	95	92	92
PPV %	81	75	
NPV %	94	95	>90

2 hour troponin? ADAPT trial

Than et al. Lancet 2011

- 1,975 patients in Asia-Pacific region with possible ACS symptoms.
- Accelerated diagnostic protocol used to identify low risk patients:
  - TIMI score = 0
  - No new ischaemic ECG changes
  - cTnI not elevated at 0 and 2h post arrival
- 392 low risk (20% of cohort)
- 1 low risk patient went on to have MACE within 30 days (0.25%)

Conclusions from ADAPT

- 'ADP could potentially identify 20% of ED patients who could be discharged within 2-3h of presentation'.
- Flaws/Limitations of study:
  - TIMI score is not very good for low risk CP. Other scores e.g. HEART score better. Evaluation ongoing.
  - ADAPT study used a decision cutoff troponin level which was higher than guidelines, therefore they may have missed more patients than was ideal.
  - Despite the designation as low risk, 74% of the ADP negative cohort had additional investigations (mostly stress tests), 18% had therapeutic interventions, and 2% had procedural interventions.
    - This suggests that further risk stratification after the ED visit was deemed necessary

Current status of 2hr rule out

- It is unclear that a 2h rule out will be robust enough to exclude all AMI.
- Potential future solutions to this:
  - Abandon the zero-miss policy (unlikely to happen)
  - Develop a better HsTnI assay
  - More research, using newer risk scores and tests
  - Using 2hr rule out on the cohort with CP >6h prior to presentation without intercurrent illness.
- For now, not an option at Castlemaine.