Appropriate use of serum troponin testing in general practice: a narrative review

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In this article, we review the evidence regarding troponin testing in a community setting, particularly relating to new information on the utility of high sensitivity assays and within the context of contemporary guidelines for the management of chest pain and the acute coronary syndrome. For this review, we synthesised relevant evidence from PubMed-listed articles published between 1996 and 2016 and our own experience to formulate an evidence-based overview of the appropriate use of cardiac troponin assays in clinical practice. We included original research studies, focusing on high quality randomised controlled trials and prospective studies where possible, systematic and other review articles, meta-analyses, expert consensus documents and specialist society guidelines, such as those from the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. This article reflects our understanding of current state-of-the-art knowledge in this area.

Summary

- The troponin assay was designed to assist in diagnosis and improve risk stratification for people presenting to the emergency setting with symptoms suggestive of an acute coronary syndrome.
- Newly developed high sensitivity assays provide reliable detection of very low concentrations of troponin and offer earlier risk stratification of patients with possible acute coronary syndrome.
- Cardiac troponin testing in general practice should be limited to patients presenting with ischaemic symptoms that occurred more than 24 hours previously. If these patients have no high risk clinical features and a normal electrocardiogram (ECG), they may be assessed with a single troponin assay but should be referred urgently to hospital if the result is elevated.
- In patients presenting with symptoms of possible acute coronary syndrome within the preceding 24 hours, or if they otherwise have symptoms consistent with unstable angina, high risk clinical features or ECG abnormalities, a serum troponin test should not be ordered and patients should be referred immediately to an emergency department.
- When a single troponin assay is appropriate, the test should be labelled as urgent and systems must be in place to ensure the result is conveyed immediately to the medical practitioner, as it has prognostic implications and may require an urgent action plan.

What is the purpose of the serum troponin assay?

The troponin assay was designed to assist in diagnosis and improve risk stratification for people presenting in the emergency setting with symptoms suggestive of an acute coronary syndrome.[1,2] These symptoms include:

- chest, jaw, arm, upper back or epigastric pain or pressure
- nausea
- vomiting
- dyspnoea
- diaphoresis
- sudden unexplained fatigue.

As the troponin assay was not designed for use in clinical contexts outside that of a possible acute coronary syndrome, an elevated troponin level in a patient without this history, although of prognostic value, is not likely to be due to myocardial infarction unless it was caused by a clinically silent event. The troponin test result should always be interpreted with reference to symptoms, comorbidities, physical examination findings and the electrocardiogram (ECG). The degree of troponin elevation is also used for quantifying the size of myocardial infarction, although it is not well validated for this purpose.[3,4]

What are the causes of serum troponin elevation?

Unlike the earlier creatine kinase assay, which was not specific to cardiac muscle, troponins are structural proteins unique to cardiac myocytes, and any elevation represents cardiac muscle injury or necrosis. Most cardiac troponin is attached to the myofilaments, but about 5% is free in the cytosol. In acute myocardial infarction or following cardiac trauma, there is disruption of the sarcolemmal membrane of the cardiomyocyte and release of the troponin in the cytoplasmic pool. There is a delay in the appearance of troponin in serum of between 90 and 180 minutes,[5-7] which means there is a requirement for serial testing of troponin levels in hospital emergency departments. Later, there is a prolonged release of troponin from the degradation of myofilaments over 10–14 days.

It is now clear that troponin may also be released under conditions of myocardial stress without cellular necrosis (including tachyarrhythmia, prolonged exercise, sepsis, hypotension or hypertensive crisis and pulmonary embolism)[8,9] (Box 1), probably through the mechanism of stress-induced myocyte bleb formation[10] and release of a small portion of the cytoplasmic troponin pool. Elevations of troponin seen in this context are sometimes erroneously referred to as "false positives"; this is incorrect because any troponin elevation is truly abnormal and is prognostic in many clinical states outside of the acute coronary syndrome.[11]

The serum troponin assay was designed to screen patients for spontaneous, usually atherothrombotic, myocardial infarction, but under the new classification of myocardial infarction (Box 2),[12] troponin elevations associated with demand–supply imbalance have led to the new diagnostic category of type 2 myocardial infarction (which is more likely to be associated with reversible or minimal myocardial injury, rather than permanent myocardial necrosis). The prevalence of all types of myocardial infarction, particularly type 2, has been amplified by the new high sensitivity troponin assays. A rise and fall in serum troponin level is required to confirm an acute myocardial infarction, irrespective of the type

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1 Causes of serum troponin level elevation

- Acute myocardial infarction (see Box 2)
- Coronary artery spasm (eg, due to cocaine or methamphetamine use)
- Takotsubo cardiomyopathy
- Coronary vasculitis (eg, systemic lupus erythematosus, Kawasaki disease)
- Acute or chronic heart failure
- Tachyarrhythmia or bradyarrhythmia
- Frequent defibrillator shocks
- Cardiac contusion or surgery
- Rhabdomyolysis with cardiac involvement
- Myocarditis or infiltrative diseases (eg, amyloidosis, sarcoidosis, haemochromatosis)
- Cardiac allograft rejection
- Hypertrophic cardiomyopathy
- Cardiotoxic agents (eg, anthracyclines, trastuzumab, carbon monoxide poisoning)
- Aortic dissection or severe aortic valve disease
- Severe hypotension or hypertension (eg, haemorrhagic shock, hypertensive emergency)
- Severe pulmonary embolism, pulmonary hypertension or respiratory failure
- Dialysis-dependent renal failure
- Severe burns affecting > 30% of the body surface
- Severe acute neurological conditions (eg, stroke, cerebral bleeding or trauma)
- Sepsis
- Prolonged exercise or extreme exertion (eg, marathon running) ◆

of troponin assay used. Chronic stable elevations are seen in some conditions (eg, chronic heart failure) where the lack of change over time indicates that an acute process is not present. True instances of false-positive troponin elevation due to calibration errors, heterophile antibodies or interfering substances have been greatly reduced by improved analytical techniques, blocking reagents and the use of antibody fragments.

What is different about the new high sensitivity troponin assays?

The newly developed high sensitivity assays provide reliable detection of very low concentrations of troponin and therefore offer earlier risk stratification of patients with possible acute coronary syndrome (3 hours after an episode of chest pain).[7] The high sensitivity assays are also presented in different units (ng/L, rather than the previous μg/L), enabling the reporting of whole numbers (eg, 40 ng/L is equivalent to the earlier assay report of 0.04 μg/L).

By expert consensus, the assay must have a coefficient of variance of < 10% at the 99th percentile value of a reference population,[13] which is the cut-off used for elevation. The benefit of the improved precision of the new high sensitivity assays is that even small elevations above this cut-off can be considered a true elevation, rather than an artefact of the assay. Examples of cut-off for elevation (> 99th percentile of a reference population) include a high sensitivity troponin T (hsTnT; Roche Elecsys) level of 14 ng/L, and a high sensitivity troponin I (hsTnI; Abbott Architect) level of 26 ng/L (these values may differ between pathology laboratories). It has been suggested that sex-specific cut-off values should be provided,[12] and, in Australia, laboratories reporting the hsTnI assay often use these differing cut-offs (female, 16 ng/L; male, 26 ng/L).

A study in an Australian hospital found that use of the high sensitivity assays was associated with significantly earlier diagnosis and less time spent in the emergency department, but did not change the revascularisation rate or reduce mortality.[14] A recent meta-analysis demonstrated that about 5% of an asymptomatic community population had an elevated serum troponin level when tested using a high sensitivity assay,[11] clearly different to the reference population (screened to exclude comorbidities) that was used to derive the assay cut-off. Even in this asymptomatic cohort, an elevated troponin level had prognostic significance and was associated with a threefold greater risk of adverse cardiac outcomes compared with people with normal troponin levels. This reflects a greater hazard than identified previously for those with elevated cholesterol (risk ratio [RR], 1.9) or diabetes, (RR, 1.7) or even from smoking (RR, 1.68).[15]

As older patients (aged ≥ 65 years) have a high prevalence of elevated troponin levels, a higher troponin cut-off has been proposed for this group.[16,17] More than 50% of patients with heart failure have elevated high sensitivity troponin levels, and the level is correlated with prognosis.[18] It has also been shown in a large cohort of patients with chronic atrial fibrillation who were taking anticoagulant therapy[19] that troponin elevation was

2 The new classification of myocardial infarction (MI)[12]

Type	Clinical situation	Definition
1	Spontaneous	MI related to ischaemia from primary coronary event such as plaque rupture, erosion, fissuring or dissection
2	Demand–supply imbalance	MI related to secondary ischaemia due to myocardial oxygen supply–demand imbalance such as spasm, anaemia, hypotension or arrhythmia
3	Sudden death	Unexpected cardiac death, perhaps suggestive of MI, but occurring before blood samples can be obtained
4a	PCI	MI associated with PCI procedure
4b	Stent thrombosis	MI associated with stent thrombosis, as seen on angiography or autopsy
5	CABG	MI associated with CABG

CABG = coronary artery bypass grafting. PCI = percutaneous coronary intervention. ◆

independently related to the long term risk of cardiovascular events and cardiac death.

When should a general practitioner measure serum troponin and what should be done if a high serum troponin level is found?

Patients who present with a history of a possible acute coronary syndrome, but have been symptom-free for between 24 hours and 14 days previously, and who have no high risk features (ongoing or recurrent pain, syncope, heart failure, abnormal ECG) could be assessed with a single serum troponin test. If patients have had ongoing symptoms within the preceding 24 hours, they should be referred immediately to an emergency department for assessment.[20] For patients in whom a single troponin test is appropriate, the test should be labelled as urgent and, as the result has prognostic implications and may require an urgent action plan, a system must be in place to ensure medical notification of the result at any hour of the day or night. In this clinical context, even a small elevation in serum troponin level may indicate an acute coronary syndrome during the preceding 2 weeks, warranting urgent cardiac assessment and hospital referral.[20] However, a negative serum troponin result in the absence of high risk features does not exclude a diagnosis of unstable angina, and urgent cardiac assessment would still be appropriate if the presenting symptoms are severe or repetitive.

When should a general practitioner not measure serum troponin?

Patients presenting with a possible acute coronary syndrome with symptoms occurring within the preceding 24 hours, or with possible acute coronary syndrome more than 24 hours previously and with high risk features such as heart failure, syncope or an abnormal ECG, require further investigations.[20] These may include urgent angiography, serial troponin testing and further ECGs in a monitored environment where emergency reperfusion treatments are available. These patients should be referred and transported to a hospital emergency department by ambulance, as it is not appropriate to perform serial troponin testing of high risk patients in a community setting.[20] High risk ECG abnormalities include tachyarrhythmia or bradyarrhythmia, any ST deviation, deep T wave inversion or left bundle branch block. Serial troponin testing is required to confirm a diagnosis of myocardial infarction, and these patients may require fibrinolysis or urgent angiography and revascularisation.

Measurement of troponin in asymptomatic people is not currently recommended as the result may be problematic, with multiple possible causes and no clearly effective investigative strategies or therapies, and has to be interpreted with respect to the entire clinical context.

Case reports of appropriate and inappropriate use of troponin testing

Patient 1

A 72-year-old woman with type 2 diabetes tells you that she had 2 hours of chest tightness 4 days ago, but has been feeling well since then. Her physical examination is unremarkable, and you think her ECG is normal. You arrange for her to have an urgent serum troponin test, and the result is significantly elevated (hsTnI, 460 ng/L; female reference interval [RI], < 16 ng/L). You call a cardiologist, who arranges her immediate admission to hospital. Echocardiography shows hypokinesis of the anterior wall and apex and a left ventricular ejection fraction of 48%. Angiography shows a severe proximal left anterior descending artery lesion, which is treated with coronary stenting, and minor disease of the other arteries. She is discharged and has a good outcome.

Comment. In this setting, measurement of troponin is reasonable, as her symptoms occurred 4 days previously and she has had no further symptoms and has no high risk features.

Patient 2

A 68-year-old man presents to your surgery with a history of severe chest tightness lasting for 2 hours that morning. It has now resolved and he is pain-free 5 hours later. He has no major cardiovascular risk factors and his physical examination and ECG are normal. You do not order any other tests and arrange ambulance transport to a hospital emergency department. Testing at the hospital shows that his hsTnI level is elevated (84 ng/L; male RI, < 26 ng/L), and angiography shows severe left main coronary artery disease. He undergoes coronary revascularisation and has a good outcome.

Comment. This patient has had possible acute ischaemic symptoms within the past 24 hours. Troponin testing in a general practice setting should therefore not be performed, and the actions taken in sending this patient for urgent assessment are appropriate.

Patient 3

A 62-year-old man with no relevant past medical history presents with a history of several episodes in the past week of dull central chest pain lasting 5–10 minutes; the latest episode was 3 days ago. His physical examination and ECG are considered normal. An urgent serum troponin assay is performed and the result is normal (hsTnI, 3 ng/L; male RI, < 26 ng/L). You are worried that his clinical presentation may still be consistent with unstable angina. You contact a cardiologist, who arranges a stress echocardiogram the following day, which is strongly positive. The patient is admitted and is found to have severe three-vessel coronary artery disease. He undergoes revascularisation, with a good outcome.

Comment. This patient presents with symptoms suggestive of unstable angina. In this setting, irrespective of any troponin values, further urgent assessment is required.

Patient 4

A 52-year-old obese man with controlled hypertension has had multiple episodes in the past 12 months of prolonged retrosternal burning pain. These have often lasted several hours and are particularly worse after meals and when recumbent. He has had no symptoms for the past 4 days. His physical examination and ECG are normal. A serum troponin test result is normal. You arrange a stress echocardiogram, which is normal, and an upper gastrointestinal endoscopy, which shows severe reflux oesophagitis. He commences taking proton pump inhibitors and has good control of his symptoms.

Comment. The symptoms of cardiac ischaemia are often atypical. In the absence of recent symptoms, consideration of a cardiac cause of this patient's presentation is essential and, in the context of this case, a single troponin test is appropriate.

Patient 5

A 58-year-old formerly well woman presents to you immediately after a 1-hour episode of burning central chest discomfort, which resolved spontaneously. She has experienced minor chest pain

episodically for the past 3 days. Her physical examination and ECG are normal. It is 7 pm; you order a serum troponin test and give her a referral for an upper gastrointestinal endoscopy. As you leave the surgery, you turn off your mobile phone so that you will not be interrupted, as you are going to the cinema. When you turn your phone on later that evening, you have two messages. The first message tells you that the troponin test result showed an elevated level (hsTnI, 43 ng/L; female RI, < 16 ng/L). The second message is from your patient's husband, who says your patient developed severe chest pain at home and they were uncertain what to do. Upon calling her husband, he tearfully says that she had a cardiac arrest at home and did not survive.

Comment. A number of concerns arise in this case. First, the troponin test should not have been ordered as there was a significant clinical suspicion of an acute coronary syndrome and, with symptoms within the past 24 hours, the patient is considered potentially at high risk and should have been urgently referred to hospital, where serial ECGs, troponin testing and risk stratification could be performed in the safety of a fully equipped emergency department. Second, whenever troponin testing is used, systems must be in place for the result to be conveyed urgently to the medical practitioner[21] and appropriate action taken.

Conclusions

Acute coronary syndrome remains a major cause of death and long term morbidity. For patients presenting to a general practice with possible acute coronary syndrome within the preceding 24 hours, including symptoms consistent with either unstable angina or high risk clinical features, a serum troponin test should not be ordered. Instead, these patients should be referred to an emergency department for evaluation in a monitored environment capable of offering defibrillation, urgent fibrinolysis or revascularisation. However, patients presenting with ischaemic symptoms that occurred more than 24 hours previously, who are now symptom-free and have no high risk features, may be assessed with a single troponin assay and referred urgently to hospital if the result is elevated. If the troponin result is negative, unstable angina is not excluded and urgent or semi-urgent cardiac referral may still be appropriate, depending on the timing and severity of symptoms. When troponin assays are used, systems must be in place for the result to be conveyed urgently to a medical practitioner so that appropriate action may be taken.

Future directions

Further refinement of strategies that use high sensitivity troponin assays may improve upon the current 3-hour rule-out time for acute myocardial infarction. Other methods of early risk stratification, including imaging techniques, are currently being evaluated. In the future, troponin levels may also prove to be useful in many clinical contexts, including gauging cardiotoxicity with chemotherapeutic agents, identifying cardiac allograft rejection or monitoring patients with heart failure. In addition, there is potential for troponin testing to be included in newer models of general cardiovascular risk stratification, but until further evaluation in prospective trials demonstrates a clinical benefit, troponin should not be measured in asymptomatic individuals.

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