# Cardiac markers

## Introduction

Cardiac markers or, more correctly, cardiac biomarkers are now integral to diagnostic and management strategies in cardiovascular disease. Scarcely a week passes without another publication claiming a new and allegedly useful cardiac biomarker. The actuality is that only two cardiac biomarkers are currently in routine clinical use; the measurement of the cardiac troponins for the differential diagnosis of suspected acute coronary syndromes and measurement of B type natriuretic peptide (BNP) for the differential diagnosis of suspected cardiac failure.

## Differential diagnosis of suspected acute coronary syndromes

Acute myocardial infarction was not recognized as a clinical entity but was a post-mortem diagnosis until 1912 when Herrick proposed that acute myocardial infarction was not always fatal and could actually be recognized during life.

Acute myocardial infarction occurs as a result of rupture or less commonly erosion of an atheromatous plaque with exposure of the plaque core. This results in initial platelet aggregation and fibrinogen accumulation, and then formation of 'white thrombus', which produces partial occlusion of the arterial lumen. The platelet aggregate is unstable and fragments may break off producing downstream platelet emboli in small vessels. The ruptured plaque may heal or the platelet aggregate may progress to activation of the clotting cascade. Activation of the clotting cascade converts fibrinogen to fibrin and produces total occlusion of the vessel by 'red thrombus'. The occlusion of the vessel reduces tissue oxygen delivery downstream – ischaemia – which if prolonged will result in cell death – infarction.

All biomarker tests aimed at detecting tissue damage are based on the same premise. When damage to tissue occurs, the cytoplasmic and structural components of the cell are released into the surrounding tissue. These then diffuse via the lymphatics and capillaries into the circulation and can then be detected in the blood. Historically, for myocardial infarction, the first tests measured non-specific cytoplasmic enzymes such as aspartate transaminase and lactate dehydrogenase. This was followed by more muscle-specific enzymes such as creatine kinase and its more (but not completely) cardiac-specific MB isoenzyme, CK-MB. These have been replaced by measurement of cardiac-specific proteins, the cardiac troponins.

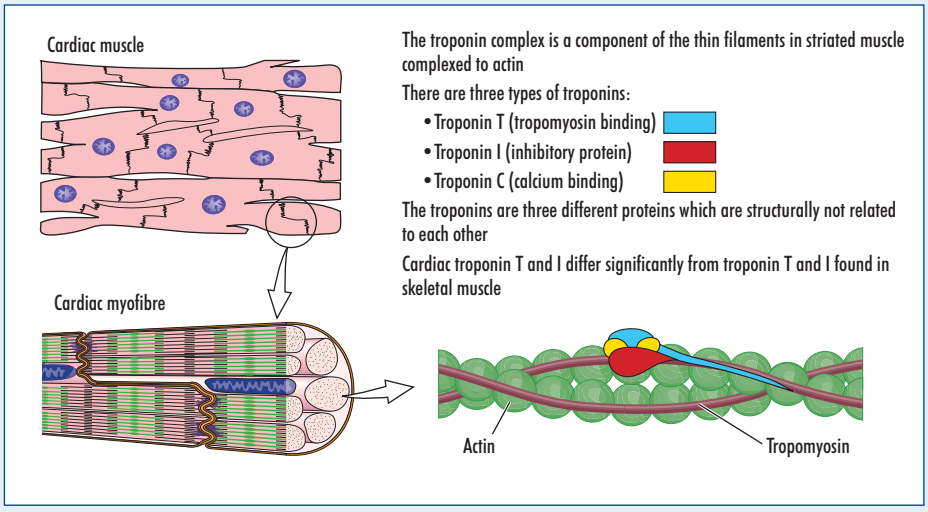
The cardiac troponins form part of the cardiac contractile apparatus, the troponin–tropomyosin complex (*Figure 1*). This is found within the sarcomere of all types of striated, but not smooth, muscle. The troponin–tropomyosin complex regulates muscle contraction. It comprises three troponins, troponin C (TnC), troponin I (TnI) and troponin T (TnT) plus tropomyosin. The complex resembles a tadpole with a globular head (a dumb-bell-shaped TnC, a globular TnI and the C terminal region of TnT) and a tail (the N terminal region of TnT). The function of TnT is structural, binding to tropomyosin and TnC.

Commercially available assays suitable for routine use have been developed for two proteins of the troponin–tropomyosin complex, cardiac troponin T (cTnT) and cardiac troponin I (cTnI). There is only a single cTnT method so results from all laboratories that measure cTnT can be compared, but there are a number of different non-standardized cTnI methods, so cTnI methods have different reference intervals. It is important that you are aware not only which method your local laboratory uses but also that laboratory results coming from a different hospital may have a different reference interval to the one that you are used to.

Cardiac troponin measurements have two advantages over other tests of myocardial injury: they are highly specific and very sensitive. Cardiac troponin is entirely specific for myocardial injury. The high specificity of cardiac troponin measurements means that in conditions where skeletal muscle injury can occur, such as multiple trauma or rhabdomyolysis, if cardiac troponin is not elevated, myocardial damage can be excluded. The high sensitivity of cardiac troponin measurements means that myocardial injury can be detected in patients with ischaemic heart disease which was previously missed.

There is now a large and consistent body of data, confirmed by meta-analysis, showing that cTnT and cTnI measurements are diagnostic and prognostic in patients presenting with chest pain (Heidenreich et al, 2001). Risk is proportional to the degree of both cTnT and cTnI elevation (Antman et al, 1996; Stubbs et al, 1996). The value of cardiac troponin measure-

***Figure 1. Structure of the troponin–tropomyosin complex.***

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ment as the central biochemical test for diagnosis of acute myocardial infarction has been recognized in the universal definition of myocardial infarction (Thygesen et al, 2007) (*Figure 2*). This defines a troponin above the upper limit of normal (the upper reference limit) as being indicative of cardiac necrosis. The definition of myocardial infarction requires evidence of cardiac necrosis in the presence of appropriate clinical findings.

## Using cardiac troponin measurements in routine clinical practice

The electrocardiogram (ECG) is the first diagnostic test in patients with chest pain. This enables division of patients into two groups, those with characteristic ECG changes of acute myocardial infarction – probable ST segment elevation myocardial infarction (STEMI) acute coronary syndrome and those with probable non-ST segment elevation myocardial infarction (NSTEMI) acute coronary syndromes.

### Probable ST segment elevation myocardial infarction acute coronary syndrome

Patients with STEMI require consideration for immediate revascularization by cardiac catheterization and angioplasty. Although ST segment elevation has a high specificity for acute myocardial infarction, not all patients with ST segment elevation have acute myocardial infarction. Cardiac troponin measurements should be used as part of the routine assessment of patients with ST segment elevation to audit diagnostic accuracy. Cardiac troponin should be measured at 12 hours from admission to confirm diagnosis and to provide quantitative evidence of the degree of cardiac damage. There is currently no evidence that cardiac troponin measurement should be used for initial diagnosis or to select patients for revascularization.

***Figure 2. The universal definition of myocardial infarction. From Thygesen et al (2007).***

Detection of the rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th centile of the upper reference limit together with evidence of ischaemia with at least one of the following:

- Symptoms of ischaemia
- Electrocardiogram changes of new ischaemia (new ST segment or T wave changes or new left bundle–branch block)
- Development of pathological Q waves in the electrocardiogram
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

### Probable non-ST elevation myocardial infarction acute coronary syndrome

Unfortunately, as few as 10% of patients presenting to hospital with chest pain have characteristic ECG changes of acute myocardial infarction. The role of cardiac biomarkers is for diagnosis and risk stratification of these 90% (or more) of patients who present with chest pain but without characteristic ECG changes. Cardiac troponin measurement is part of the assessment of the patient and should be used to complement, not replace, clinical and ECG findings.

The current recommendation for measurement of cardiac troponin is that a measurement should be performed on admission and 10–12 hours later.

Modern troponin assays are very sensitive and can measure values down to within the reference interval. This is a recent development and such assays are not yet in use in every hospital but will become the norm. Using one of the modern more sensitive assays diagnosis can be accelerated with a sample taken on admission and 6 hours from admission. A rise in troponin from the 0- to the 6-hour sample indicates myocardial infarction is occurring and should be followed up by a third sample at 12 hours to confirm the diagnosis. If there is no change between the admission and 6-hour sample, myocardial infarction is unlikely. Such patients should then be assessed and considered for stress electrocardiography or other non-invasive cardiac imaging to exclude a flow-limiting stenosis.

If clinical suspicion is high or the patient has further chest pain or dynamic ECG changes, a further troponin measurement is indicated 12 hours from admission (6 hours from the last sample). Patients with chest pain and/or ECG changes and a rising troponin require treatment with antithrombotic agents and consideration for cardiac catheterization.

### Troponin elevation in non-acute coronary syndromes patients

An elevated cardiac troponin level is absolutely specific for myocardial injury but myocardial injury can occur in other situations than myocardial infarction. Myocarditis can often mimic STEMI on the ECG and is associated with an elevated troponin level as a result of myocardial injury. It is not, however, a myocardial infarction. To diagnose a myocardial infarction there must be a change in the cardiac troponin level together with clinical or ECG evidence. If the diagnosis is unclear cardiac imaging may be helpful.

There is a very large range of clinical conditions which can cause troponin rises but are not acute myocardial infarction. Medical conditions where troponin elevation occurs may be clinically divided into those associated with a primary ischaemic myocardial injury, with a secondary ischaemic cardiac injuries and those with a non-ischaemic cardiac injury. Primary ischaemic myocardial injury is classic myocardial infarction. Secondary ischaemic cardiac injury occurs when myocardial damage occurs on a background of underlying coronary disease, and non-ischaemic cardiac injury is where there is direct myocardial injury (*Table 1*).

In all cases where outcome has been examined, an elevated cardiac troponin level in a non-acute coronary syndromes patient has been found to be associated with a worse prognosis. One of the best documented examples of this is patients with chronic renal failure where elevation of both cTnT and cTnI occurs and which is associated with an increased risk of death.

## Natriuretic peptides

The natriuretic peptides form a family of highly conserved bioactive peptides with effects on sodium and water balance. These effects may be systemic, autocrine or paracrine or a combination of all three according to which type of natriuretic peptide. In man, three natriuretic peptides are found. Atrial natriuretic peptide (ANP) is found in storage granules in the atria. Release occurs in response to changes in vascular pressure. B type natriuretic peptide (BNP), originally known as brain type natriuretic peptide, is found in both atria and ventricles and is produced in response to tension in the atrial and ventricular walls. C type

**Table 1. Examples of secondary and non-ischaemic myocardial injury**

| | | | |
|---|---|---|---|
| Secondary ischaemic cardiac injury | Coronary intervention | Primary percutaneous intervention | Distal embolization from atheroma or debris |
| | | | Side branch occlusion |
| | | Elective percutaneous intervention | Distal embolization or debris |
| | | | Side branch occlusion |
| | | Coronary artery bypass graft | Global ischaemia from inadequate perfusion, myocardial cell production of anoxia |
| | Sympathomimetics | Cocaine abuse | |
| | | Catecholamine storm | Head injury, stroke, intracerebral bleeding |
| | Pulmonary embolus | Presumed right heart strain or hypoxia | |
| | Coronary artery spasm | In Japan – up to 10% of admissions for chest pain | |
| | Coronary artery embolization | Clot | |
| | | Air | |
| | | Coronary artery bypass graft | |
| | Coronary artery inflammation with microvascular occlusion | Vasculitidies | |
| | | Connective tissue damage (e.g. Pompe's disease) | |
| | | Systemic lupus erythematosus | |
| | End-stage renal failure | More severe coronary artery disease, but 50% of end-stage renal disease patients have normal coronaries | |
| | Rhythm disorders | Prolonged tachycardia or bradycardia with ischaemic heart disease | |
| | Acute heart failure | Only if caused by ischaemic heart disease | |
| | Chronic heart failure | | |
| | Direct coronary trauma | | |
| | Extreme endurance exercise | Extreme marathons | Wall motion abnormalities |
| | | Extreme training | Cardiac troponin-positive deaths presumed to be caused by extreme oxygen debt producing ischaemia |
| Non-ischaemic cardiac injury | Known causes of myocarditis | Infection | Bacterial or viral |
| | | | Rheumatic myocarditis |
| | | | Septic shock |
| | | | Acute pericarditis |
| | | Inflammation | |
| | | Autoimmune | Polymyositis |
| | | | Scleroderma |
| | | | Sarcoidosis |
| | | Drug-induced | Alcohol |
| | | | Cocaine abuse |
| | | | Chemotherapy |
| | | Toxins | Snake, puffer fish envenomation |
| | Cardiac trauma | Direct | Road traffic accident |
| | | | Stabbing |
| | | Cardiac surgery | |
| | Metabolic/toxic | Renal failure | |
| | | Multiple organ failure | |

natriuretic peptide (CNP) is produced by the endothelial cells as a vasodilator. Currently, only routine measurement of BNP can be performed so ANP and CNP will not be discussed further.

Unlike many other hormones, BNP is not stored but undergoes continuous transcription and translation. Increase in wall tension stretches the cardiac myocytes and results in up-regulation of BNP production. BNP is secreted as a prohormone, pro-BNP. This then undergoes cleavage to produce the N-terminal fragment of the prohormone, N-terminal pro-BNP (NTproBNP) and the active BNP. Clearance of BNP is by a clearance receptor and the action of neutral endopeptidase. There is some renal clearance of BNP and NTproBNP. Renal impairment causes increase in both BNP and NTproBNP levels.

BNP and NTproBNP measurement are diagnostically equivalent. Measurement of NTproBNP is standardized but BNP values vary between laboratories. NTproBNP is a more stable molecule so it is more suitable for primary care applications. Both BNP and NTproBNP values are affected by age and gender. Levels are increased with increasing age and are higher in women than men. The role of BNP and NTproBNP measurement is in the diagnosis of patients with suspected heart failure. This can be divided into two clinical scenarios.

## Differential diagnosis of acute breathlessness

In patients presenting to the emergency department with acute shortness of breath the measurement of BNP or NTproBNP provides a diagnostically efficient strategy for differential diagnosis (Maisel et al, 2002; Januzzi et al, 2006). A low BNP or NTproBNP virtually excludes heart failure as a cause of breathlessness. A markedly elevated BNP or NTproBNP indicates that heart failure is the likely cause. However, a number of other clinical conditions (including infection) will cause BNP and NTproBNP to be elevated. A grey zone of values which neither rule in or rule out acute heart failure exists (*Table 2*).

## Differential diagnosis of heart failure in primary care

The primary care diagnosis of heart failure is unreliable with a misdiagnosis rate of as high as 66%. This may result in inappro-

priate referral to secondary care for echocardiography or for outpatient assessment. Measurement of BNP or NTproBNP in primary care can be used to reliably exclude heart failure as a cause of breathlessness or ankle swelling (*Table 2*) and so prevent unnecessary echocardiography (Groenning et al, 2004).

## Conclusions

Measurement of cardiac troponin, either cTnT or cTnI, is the gold standard biochemical test for the detection of myocardial injury and for the diagnosis of myocardial infarction. It has replaced all other tests for this purpose. However, the diagnosis of myocardial infarction remains clinical. An elevated cardiac troponin level is required for the diagnosis of myocardial infarction but only in the appropriate clinical context. B type natriuretic peptide measurements either as BNP or NTproBNP provide useful additional information in clinical assessment when heart failure is suspected. BJHM

*Conflict of interest: none.*

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**Table 2. BNP and NTproBNP values for the differential diagnosis of heart failure**

| | Value below which chronic heart failure is unlikely (ng/litre) | | Indeterminate zone (ng/litre) | | Value above which acute heart failure is very likely (ng/litre) | |
|---|---|---|---|---|---|---|
| Age | BNP | NTproBNP | BNP | NTproBNP | BNP | NTproBNP |
| <60 years | 40 | 50 | 40–100 | 50–450 | 100 | 450 |
| 60–75 years | 40 | 100 | 40–100 | 100–900 | 100 | 900 |
| >75 years | 40 | 250 | 40–100 | 250–1800 | 100 | 1800 |

BNP= brain type natriuretic peptide; NTproBNP = N-terminal pro-brain type natriuretic peptide. From Maisel et al (2002); Fuat et al (2006); Januzzi et al (2006); Hildebrandt and Collinson (2008)

## KEY POINTS

- An elevated cardiac troponin level, either cardiac troponin T or cardiac troponin I, is required for the diagnosis of myocardial infarction.
- Although an elevated cardiac troponin T or cardiac troponin I level is specific for cardiac damage, cardiac damage may have other causes. The diagnosis of myocardial infarction therefore requires additional clinical features.
- Measurement of B type natriuretic peptide either as BNP or NTproBNP is useful for the differential diagnosis of suspected acute and chronic heart failure.