Measurement of troponin in cardiomyopathies

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Abstract

Troponins are thin myofilament proteins that regulate the contraction of cardiac and skeletal muscle. The cardio-specific troponin I (TnI) and T (TnT) proteins are sensitive and specific biomarkers of myocardial injury which over the past twenty years have revolutionised the diagnosis and management of myocardial infarction. With the advent of high sensitivity assays the role for cardiac troponins is possibly expanding. Elevated levels are associated with adverse cardiovascular events and mortality in heart failure and the general population. Studies in cardiomyopathies are generally small with <200 patients, but serum troponin levels can be chronically raised and detect subclinical myocyte damage. This review examines all major published studies of cardiac troponin measurement in cardiomyopathies. There is considerable variability among studies regarding assays used and definitions of abnormal results but elevated troponin levels are almost invariably related to poor prognosis and their negative predictive value is important.

Troponin and the heart

The discovery of troponin

The discovery of actin and the actomyosin system in the 1940s provided a model with which to study the components involved in the contraction and relaxation cycle of muscle.1 It soon became apparent that adenosine triphosphate (ATP) was essential for this process2 and later that calcium was required for the activation of the MgATPase of the myofilaments.3 In 1972 troponin was demonstrated to be essential for the regulation of cardiac muscle.4 By 1972, troponin was demonstrated to be a complex of three proteins, troponin C, I and T.5,6 Subsequent developments revealed that each protein is under the control of individual genes and has isoforms specific to the muscle type. Over the last 20 years cardiac troponins have emerged as sensitive and specific biomarkers of myocardial injury and transformed the management of myocardial infarction (Figure 1).

Troponin genes

Several troponin genes (Table 1) have been described based on molecular cloning in humans and other vertebrates. Each of these genes is subject to alternative splicing, resulting in the production of multiple tissue-specific isoforms. Mutations in all the troponin genes expressed in the heart have been linked to familial cardiomyopathies (Table 2).

Troponin proteins

The troponin genes encode different protein isoforms, which are expressed in a tissue-specific manner (Table 3). Two troponin genes, TNNI3 and TNNT2 are highly specific to cardiac tissue encoding cardiac troponin I (TnI) and T (TnT) respectively. Although only one protein isoform has been described for TNNI3, 12 different isoforms have been described for TNNT2 and are produced by alternative splicing.7 Isoform 6 predominates in normal adult heart. Isoforms 1, 7 and 8 are expressed in fetal heart. Isoform 7 is also expressed in failing adult heart. The fetal heart shows a greater expression of TNNI3 in the atrium than in the ventricle, while the adult heart shows a greater expression of TNNI3 in the ventricle than in the atrium.8 Together these cytoplasmic troponin proteins form a regulatory troponin complex which interacts with actin and alpha tropomyosin in the thin filament of skeletal and cardiac muscle sarcomeres.9

Cardiac troponins as clinical biomarkers

Troponins transiently leak out of the myocyte when it is damaged, for example by acute ischaemia. They have therefore been used as biomarkers of myocardial injury and their release kinetics make them particularly suitable for diagnosis of acute coronary syndromes.10,11 Cardiac troponins have also shown some potential as predictors of disease progression and mortality in other cardiac conditions such as aortic stenosis,12 stable coronary artery disease13 and chronic heart failure.14

Development of clinical troponin assays

Immunoassays for TnI and TnT were developed in the 1980s.12,15 Troponins proved to be more specific for cardiac damage and more persistently elevated [thus allowing for the diagnosis of later acute coronary syndrome (ACS) presentations] than competing cardiac biomarkers such as creatine kinase MB.12,18

Mounting evidence led the European Society of Cardiology and American College of Cardiology to describe troponins as the preferred marker for myocardial injury and formal inclusion in clinical practice guidelines in 2000.19,20 The early assays were refined to decrease the rate of false-negative results in the presence of anti-cardiac troponin autoantibodies.1

High sensitivity assays

The recent transition to highly sensitive troponin (hs-Tn) assays in clinical practice has encouraged the hunt for an expanded role. Whilst increased sensitivity allows for more rapid and precise diagnosis and earlier rule out of acute coronary syndrome (ACS), the major disadvantage is the potential for unnecessary, invasive and expensive investigations.22 Defining abnormal levels and interpreting results is challenging for several reasons: there are a variety of assays being produced by different manufacturers, a broad range of conditions can increase hs-Tn and even healthy individuals can have elevated levels.22,24

Value of troponin measurement in cardiomyopathies

Whilst mutations in the troponin genes are well recognised to cause cardiomyopathy, measurement of the protein in plasma or serum is gaining increasing attention as useful biomarkers to stage cardiovascular disease, stratify treatment and predict prognosis.
It is not entirely clear why myocardial diseases should cause troponin release into the circulation. One theory is that myocyte ischaemia and necrosis result from an imbalance between the increased demands of the myocardium and its blood supply; the other is that the underlying genetic abnormalities themselves cause cellular injury and subsequent leakage of myocyte contents.25 There are several studies describing chronic troponin elevation in cardiomyopathies implying ongoing sub-clinical myocyte necrosis, apoptosis or leakage.26-28

In this section, we summarise the clinical studies that have examined the role of serum troponin measurement in each of the cardiomyopathies. We performed a comprehensive literature search by using electronic bibliographic databases (MEDLINE, EMBASE and The Cochrane Library) and combinations of the following keywords: troponin, biomarker, hypertrophic, obstructive, dilated, restrictive, Fabry, non-compaction, amyloid, peri-partum, arrhythmogenic and cardiomyopathy. Bibliographies of all selected articles and review articles were reviewed for other relevant articles.

### Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited heart muscle disorder with a prevalence of 1 in 500.29,30 Clinically it is defined as left ventricular hypertrophy (LVH) unexplained by loading conditions.31 Most disease-causing genes encode for proteins of the cardiac sarcomere with mutations in beta-myosin heavy chain, MYH7, and myosin-binding protein C, MYBPC3, accounting for much of human disease. Less commonly mutations in cardiac troponin genes (TNNI3, TNNT2 and TNNC1) cause HCM. Inheritance is usually autosomal dominant with variable penetrance, however mutations can arise de novo and up to 40% of patients have no identifiable mutation.32 Family screening forms an integral part of clinical assessment, and the disease spectrum now extends to asymptomatic adults and children who carry a pathogenic mutation; these patients may have a sub-clinical phenotype with mild or no clinically detectable abnormalities.33 The frequency of patients with no identifiable mutation or symptoms, and HCM’s phenotypic resemblance to other conditions such as athletic or hypertensive LVH can make diagnosis and screening difficult. Non-genetic biomarkers therefore have a potential role in differentiating HCM from other conditions, as well as staging and predicting prognosis. High sensitivity cardiac troponin T (hs-TnT) are associated with cardiovascular events, heart failure and death in HCM and Tn measurement is recommended as part of a laboratory work up.34 Levels are higher than in hypertension but lower in infiltrative conditions such as amyloidosis.35,36

#### Prevalence: Increased levels of Tn (usually defined as being above the manufacturer’s recommended 99th percentile cut-off point) have been reported in between 4% and 66% of patients with HCM (Table 4). By comparison, prevalence of elevated Tn in the general population is 0.7% using a traditional lower sensitivity TnT assay37 and up to 4% using a hs-Tn
Exercise can increase Tn levels.\textsuperscript{38} 

Clinical correlates: troponin elevation in HCM is associated with greater LV wall thickness\textsuperscript{37,43} and LV mass.\textsuperscript{44-46} Two studies found Tn elevation in patients with LV outflow tract obstruction\textsuperscript{37,42} but another found no correlation.\textsuperscript{40} The natural history of HCM includes progression to heart failure and Tn elevation is present in those with LV systolic dysfunction\textsuperscript{37,40,41} although the degree of hs-TnT elevation does not correlate linearly with ejection fraction.\textsuperscript{31} The relationship with New York Heart Association (NYHA) heart failure class however is conflicting.\textsuperscript{37,40} Diastolic dysfunction, usually an earlier feature in HCM is also associated with Tn release. Several studies report correlations between Tn and left atrial (LA) area or diameter\textsuperscript{37,42,46} as well as filling pressure measured by the ratio between early diastolic mitral inflow velocity and early diastolic mitral annular velocity (E/EA)\textsuperscript{40,42}. It is uncertain whether Tn can help detect the presence of paroxysmal atrial fibrillation (AF) with studies reporting both a positive\textsuperscript{41,46} and negative association.\textsuperscript{42,46} More recently Tn levels have been related to the presence and extent of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR). Individuals with elevated Tn have a higher prevalence of LGE\textsuperscript{42,44,46,49} but data are conflicting on whether Tn measurement is an independent predictor of the extent of LGE.\textsuperscript{41,49,42} A high T2 signal on CMR, a potential marker of active tissue injury, in HCM is also associated with elevated troponin levels.\textsuperscript{39}

Prognosis: patients with HCM and elevated TnI have significantly more CV events (HCM-related death or hospitalisation, embolic strokes, or the appearance of sustained ventricular tachycardia) than those with normal TnI over a follow-up period of 39 months.\textsuperscript{31} An adverse prognosis has also been demonstrated using a hs-TnT assay in two independent study cohorts.\textsuperscript{43,42}

Combining measurement of cardiac troponins with natriuretic peptides may provide additional value in assessing prognosis of several cardiomyopathies. In HCM, Brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) correlates with similar clinical parameters to Tn,\textsuperscript{44,46,48,51,52} but was superior to hs-TnT at predicting which unaffected gene mutation carriers would go on to develop HCM.\textsuperscript{44} To date there are few biomarker studies in pre-phenotypic disease in any cardiomyopathy.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment.\textsuperscript{31} It is a non-specific phenotype and the result of a wide range of cardiac insults.\textsuperscript{50} Approximately half of cases are deemed to be idiopathic.\textsuperscript{34} Many idiopathic presentations have an underlying genetic basis and unlike HCM, where relatively few mutations predominate, DCM can be caused by defects in over 60 genes.\textsuperscript{27} The common effects of these mutations are hypo-contractile cardiac myocytes, which lead to the characteristic ventricular dilatation and thinning.

Prevalence: While Tn is often raised in idiopathic DCM, several studies have shown that it is lower than in myocarditis and TnT but not hs-TnT might be useful in distinguishing these conditions\textsuperscript{42,41} (Table 5). Patients with ischaemic cardiomyopathy have greater levels of TnI than DCM patients at hospital presentation but levels are more likely to remain elevated at 3 months in DCM.\textsuperscript{27,42}

Clinical correlates: the relationship between Tn and imaging parameters in DCM is less consistent than in HCM. Elevated Tn is associated with increased LV diameters and volumes but not always with ejection fraction.\textsuperscript{56,33,64}  However, over 5 years of follow-up, elevated hs-TnT predicted a fall in LV ejection fraction.\textsuperscript{25} As for LGE, an independent predictor of mortality in DCM,\textsuperscript{66} only one study has investigated its relationship with Tn, finding that hs-TnT could predict LGE extent but TnT could not.\textsuperscript{40} Elevated troponin levels and the presence of myocardial infarction on CMR are predictors of LV recovery in children presenting with dilated cardiomyopathy.\textsuperscript{59}

Prognosis: The relationship between troponin and prognosis in DCM appears to depend on assay sensitivity. Four studies\textsuperscript{39,28,45,58} found an association between TnT elevation and CV morbidity and mortality while three did not.\textsuperscript{40,45,59} Similarly, for Tn, three studies reported an association\textsuperscript{27,36,43} while two did not.\textsuperscript{51,52} Only hs-TnT has been found thus far to be an independent predictor of adverse cardiovascular events in all the studies that have examined it.\textsuperscript{30,57,70} The largest study describes mortality in 310 patients admitted to hospital for decompensation of heart failure due to underlying DCM; mortality over 2.2 years was significantly higher in patients with elevated TnI compared to those with normal TnI at baseline.\textsuperscript{41} The longest follow-up study over 5.1 years describes significantly more CV events in patients with elevated TnI or hs-TnT, but not TnI.\textsuperscript{45}

Overall, the most promising role for Tn in DCM is in prognostication. This fits with the role troponins have in heart failure more broadly, where higher levels have been associated with poorer clinical outcomes.\textsuperscript{51,52}

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness.\textsuperscript{31} Familial RCM is much more rarer than HCM and DCM and no systematic studies of Tn measurement have been reported. Restrictive physiology can occur in a wide range of different pathologies including amyloid, Anderson Fabry disease and Chagas cardiomyopathy which are discussed below.\textsuperscript{55}

Non-compaction cardiomyopathy

Left ventricular non-compaction (LVNC) is a challenging condition to diagnose and there is overlap both in the genetics and phenotype with other cardiomyopathies.\textsuperscript{31} A retrospective study of 71 patients found TnT was elevated in 12 (17%) patients with LVNC and was associated with the presence of neuromuscular disease and a worse prognosis.\textsuperscript{71} An observational study of 50 patients with LVNC, stratified by ejection fraction, found elevated levels of TnI and TnT in both individuals with preserved (LVEF > 50%, n=24) and reduced (LVEF <35%, n=26) ejection fraction compared with controls.\textsuperscript{75}

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined histologically by the presence of progressive replacement of right ventricular myocardium with adipose and

<table>
<thead>
<tr>
<th>UniProt Identifier</th>
<th>Protein name</th>
<th>Protein Isoforms</th>
<th>Mass (kDa)</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>P45379</td>
<td>Troponin T, cardiac</td>
<td>12</td>
<td>37</td>
<td>Binds troponin complex to tropomyosin</td>
</tr>
<tr>
<td>P19429</td>
<td>Troponin I, cardiac</td>
<td>1</td>
<td>22.5</td>
<td>Binds actin and inhibits actomyosin ATPase activity</td>
</tr>
<tr>
<td>P63316</td>
<td>Troponin C, cardiac and skeletal</td>
<td>1</td>
<td>18</td>
<td>Binds Ca\textsuperscript{2+} to a low affinity Ca\textsuperscript{2+}-specific binding site relieving the Tn inhibition</td>
</tr>
<tr>
<td>Year</td>
<td>1st author</td>
<td>Biomarker</td>
<td>Population</td>
<td>Frequency of Tn elevation</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>2003</td>
<td>Sato</td>
<td>TnT</td>
<td>30 HCM</td>
<td>12/30 (40%)</td>
</tr>
<tr>
<td>2006</td>
<td>Pop</td>
<td>TnI, TnT</td>
<td>7 HCM</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>2006</td>
<td>Taniguchi</td>
<td>TnT BNP</td>
<td>22 HCM</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td>2010</td>
<td>Kubo</td>
<td>TnI, BNP</td>
<td>182 HCM</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Moreno</td>
<td>hs-TnT</td>
<td>95 HCM</td>
<td>40/95 (42%)</td>
</tr>
<tr>
<td>2011</td>
<td>Kubo</td>
<td>TnI, BNP</td>
<td>107 HCM</td>
<td>107/162 (66%)</td>
</tr>
<tr>
<td>2013</td>
<td>Okamoto</td>
<td>hsTnT BNP and CK</td>
<td>73 HCM</td>
<td>19/73 (26%) 0/73 (73%)</td>
</tr>
<tr>
<td>2013</td>
<td>McGorrian</td>
<td>TnI</td>
<td>24 borderline HCM</td>
<td>TnI 3/17 (18%) hsTnI 4/19 (21%)</td>
</tr>
<tr>
<td>2013</td>
<td>Kawasaki</td>
<td>hs-TnT BNP and CK</td>
<td>53 HCM</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Kubo</td>
<td>hs-TnT</td>
<td>183 HCM</td>
<td>99/183 (54%)</td>
</tr>
<tr>
<td>2014</td>
<td>Jenab</td>
<td>hs-TnT</td>
<td>98 HCM</td>
<td>42/98 (43%)</td>
</tr>
<tr>
<td>2014</td>
<td>Cramer</td>
<td>hs-TnT</td>
<td>62 HCM</td>
<td>16/62 (26%)</td>
</tr>
<tr>
<td>2014</td>
<td>Nakamura</td>
<td>hs-TnT BNP</td>
<td>102 HCM</td>
<td>37/102 (36%)</td>
</tr>
<tr>
<td>2015</td>
<td>Kubo</td>
<td>hs-TnT BNP</td>
<td>35 HCM 8 amyloid 3 Fabry</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Zhang</td>
<td>TnI, BNP</td>
<td>149 HCM</td>
<td>42/149 (28%)</td>
</tr>
<tr>
<td>2016</td>
<td>Hamada</td>
<td>TnT CK and LDH</td>
<td>77 HCM</td>
<td>12 control 3/7 (4%)</td>
</tr>
<tr>
<td>2016</td>
<td>Zhang</td>
<td>TnI, BNP</td>
<td>163 HCM</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>Hasler</td>
<td>hs-TnT</td>
<td>91 HCM</td>
<td>46/91 (51%)</td>
</tr>
<tr>
<td>2016</td>
<td>Ho</td>
<td>hs-TnT BNP</td>
<td>38 HCM genes carriers without hypertrophy</td>
<td></td>
</tr>
</tbody>
</table>

CK, creatine kinase; LDH, lactate dehydrogenase; AF, atrial fibrillation; FS, fractional shortening; CHF, congestive heart failure; MWT, maximal left ventricular wall thickness; LVOTO, left ventricular outflow tract obstruction; LVS, left ventricular systolic dysfunction; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVEDV/LVESV, left ventricular end diastolic/systolic volume; LAA, left atrial area; NSVT, non sustained ventricular tachycardia; FH-SCD, family history of sudden cardiac death; FU, follow up.
fibrous tissue. Mutations in genes encoding for desmosomal proteins are detectable in 30-50% patients but diagnosis depends on integrating structural, histological, electrocardiographic, arrhythmic and genetic features.

Troponin release has not been systematically evaluated in this disease but there are case reports of troponin elevation associated with ventricular arrhythmia in the absence of coronary artery disease, postulating that Tn release may point toward a “hot” arrhythmic phase of the disease.

**Fabry cardiomyopathy**

Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disease caused by deficiency of the enzyme alpha-galactosidase. Cardiac involvement usually manifests with concentric left ventricular hypertrophy and Tn levels are typically higher than in HCM. Early diagnosis is important because enzyme replacement therapy can halt disease progression.

A persistent increase in Tn was first reported in 3 out of 14 (21%) adults with AFD all of whom had LVH and LGE on CMR studies. A larger (n=62) study from the same centre

<table>
<thead>
<tr>
<th>Year</th>
<th>1st author</th>
<th>Biomarker</th>
<th>Population</th>
<th>Frequency of Tn elevation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Sato</td>
<td>TnT</td>
<td>17 acute</td>
<td>3/17 (18%)</td>
<td>3/17 (18%) +ve TnT. Cardiac event-free rate was significantly higher for TnT type III procollagen/7S collagen -ve. CK level similar</td>
</tr>
<tr>
<td>2001</td>
<td>Sato</td>
<td>TnT</td>
<td>60 chronic</td>
<td>27/60 (45%)</td>
<td>27/60 (45%) +ve TnT initially. 17/60 (28%) maintained +ve TnT after mean 16 mo of CHF treatment - their LVDd/LV/EF worsened while they improved for the others; their cardiac event-free and survival rates were significantly worse.</td>
</tr>
<tr>
<td>2002</td>
<td>Soongswang</td>
<td>TnT</td>
<td>10 acute DCM 10 myocarditis 21 controls</td>
<td>10/60 (17%)</td>
<td>10 paediatic DCM patients had identical Tn concentrations to 21 controls, and significantly less than 10 with myocarditis. CK-MB was similarly useful for differentiating between DCM and myocarditis</td>
</tr>
<tr>
<td>2004</td>
<td>Aso</td>
<td>TnT</td>
<td>31 chronic</td>
<td>9/31 (29%)</td>
<td>TnT and Tenascin-C correlated</td>
</tr>
<tr>
<td>2005</td>
<td>Soongswang</td>
<td>TnT</td>
<td>19 acute</td>
<td>3/19 (16%)</td>
<td>TnT useful for distinguishing myocarditis from DCM (higher in former). TnT levels did not correlate with adverse outcomes in DCM (which may be due to timing of the blood sampling)</td>
</tr>
<tr>
<td>2006</td>
<td>Nellessen</td>
<td>TnI</td>
<td>33 acute</td>
<td>8/33 (25%)</td>
<td>TnI elevated in both idiopathic (n=33) and ischaemic (n=25) (&gt; in ischaemic) at baseline and after 3 months follow-up. However ischaemic CM TnI decreased, idiopathic DCM’s TnI did not. TnI was a predictor of mortality</td>
</tr>
<tr>
<td>2006</td>
<td>Taniguchi</td>
<td>TnT</td>
<td>41 mixed</td>
<td>8/41 (20%)</td>
<td>Patients being investigated for CHF 8/41 (20%) TnT +ve. 7/36 (19%) remained +ve after mean 58.7 days F/U. Significantly higher adverse CV event rates in TnT +ve (38% vs 33%) with either idopathic DCM or inflammatory CM, LGE extent correlated with hsTnT and BNP but not TnT. hsTnT could not differentiate between the CMs.</td>
</tr>
<tr>
<td>2007</td>
<td>Miller</td>
<td>TnT</td>
<td>13 chronic</td>
<td>14/15 (20%)</td>
<td>All biomarkers significantly higher in ischaemic CM vs idiopathic DCM. Baseline TnT/TnI did not predict mortality</td>
</tr>
<tr>
<td>2008</td>
<td>Miettinen</td>
<td>TnI</td>
<td>95 chronic</td>
<td>14/95 (15%)</td>
<td>14/95 (15%) TnI +ve. Consistent over mean 4.1 years F/U. LV’ dimension, volume and LV/EF correlated with TnI level. Fewer end-points (CV death, transplant, ICD) if normal TnI</td>
</tr>
<tr>
<td>2011</td>
<td>Frankenstein</td>
<td>hsTnT</td>
<td>24 chronic</td>
<td>8/24 (33%)</td>
<td>8/24 (33%) +ve hsTnT (71% for IHD)/ No correlation with LV/EF</td>
</tr>
<tr>
<td>2011</td>
<td>Kawahara</td>
<td>TnT</td>
<td>85 chronic</td>
<td>4/85 (5%)</td>
<td>4/85 (5%) TnT +ve, 46/85 (54%) hsTnT +ve. 31/85 (36%) TnT detectable, 76/85 (89%) hsTnT detectable. During median F/U 4.1 years, 20 CV deaths - hsTnT, but not TnT, was a significant prognostic predictor</td>
</tr>
<tr>
<td>2013</td>
<td>Sramko</td>
<td>TnT, hsTnT</td>
<td>27 chronic</td>
<td>7/27 (26%)</td>
<td>12/27 (44%) 7/27 (26%) TnT +ve, 12/27 (44%) hsTnT +ve. Across 42 patients with either idopathic DCM or inflammatory CM, LGE extent correlated with hsTnT and BNP but not TnT. hsTnT could not differentiate between the CMs. Across both CMs, increased hsTnT and/or BNP was associated with adverse CV events</td>
</tr>
<tr>
<td>2014</td>
<td>Li</td>
<td>TnI</td>
<td>310 acute</td>
<td>64/310 (21%)</td>
<td>64/310 (21%) +ve TnI - larger LV/Dd/LV diameters, but not LV/EF or BNP. Mean F/U 2.2 years - 24/64 (38%) +ve TnI died vs 37/246 (15%) normal TnI. No difference in CK-MB</td>
</tr>
<tr>
<td>2014</td>
<td>Bakal</td>
<td>hsTnT</td>
<td>27 chronic</td>
<td>5/27 (20%)</td>
<td>hsTnT higher in ischaemic CM than DCM, BNP was not different</td>
</tr>
<tr>
<td>2015</td>
<td>Baba</td>
<td>TnT</td>
<td>54 chronic</td>
<td>15/54 (28%)</td>
<td>17/54 (31%) TnT/Type III procollagen/7S collagen -ve. CK level similar</td>
</tr>
<tr>
<td>2015</td>
<td>Raimondi</td>
<td>TnI</td>
<td>66 acute</td>
<td>35/66 (53%)</td>
<td>Children followed for 2.2 years. TnI and CMR predicts LV recovery</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; CM, cardiomyopathy; DCM, dilated cardiomyopathy; LV/Dd/LV diameters, left ventricular diameter in diastole/systole; LVEF, left ventricular ejection fraction; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; CV, cardiovascular; ICD, implantable cardioverter defibrillator; LA, left atrial; LVDd, left ventricular diameter in diastole; LVDs, left ventricular diameter in systole; LVEF, left ventricular ejection fraction; F/U, follow up; RV, right ventricular.
Table 6. Summary of the role of troponin measurement in cardiomyopathy. Staging refers to the association of elevated troponin levels with clinical markers of advanced disease. See text for details.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence %</th>
<th>Staging</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>36 (4-66)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>27 (5-54)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>17</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Left ventricular non-compaction</td>
<td>87</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Arrhythmo genetic right ventricular cardiomyopathy</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anderson Fabry disease</td>
<td>37 (21-40)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Takotsubo cardiomyopathy</td>
<td>-</td>
<td>✓</td>
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<tr>
<td>Amyloid</td>
<td>-</td>
<td>✓</td>
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<tr>
<td>Chagas cardiomyopathy</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
<td>31</td>
<td>✓</td>
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reported elevated TnI in 37% patients and found a normal TnI level had a high negative predictive value regarding the presence of a LVH.82 This was confirmed in an independent cohort of 75 patients followed for over 3 years; elevated hs-TnI was found in 40% patients and correlated with extent and progression of LGE detected by CMR indicating it is a potential marker of cardiomyopathy progression in AFD.83 A recent study found similar associations of TnI and TnT with LGE and LVH, but also T2 mapping a technique sensitive to myocardial inflammation and oedema.84

**Takotsubo cardiomyopathy**

Takotsubo cardiomyopathy (TTC) is characterized by transient regional systolic dysfunction involving the left ventricular apex in the absence of obstructive coronary disease on coronary angiography.85 There is an increase in TnI and TnT, typically at lower levels than acute myocardial infarction, but not enough to be diagnostic. TnI and TnT are typically at lower levels than acute myocardial infarction, but not enough to be diagnostic.86 During hospitalisation Tn levels increase significantly more in acute coronary syndromes (6 fold) compared with TTC (1.8 fold).87 A large international registry of 1750 patients with TTC found Tn levels were elevated in 87% patients and an initial Tn measurement of > 10 times the upper limit of the normal level was an independent predictor of the combined end-point of serious in-hospital complications.82

**Amyloid cardiomyopathy**

Cardiac amyloidosis is caused by a group of disorders that produce an extracellular deposition of insoluble amyloid fibrils due to aggregation of misfolded proteins. The cardiac phenotype is typically either HCM or RCM and the condition may be inherited (usually due to mutations in transthyretin, TTR) or associated with immunoglobulin light-chain deposition — termed AL amyloidosis.84 Elevated cardiac Tn levels are associated with a poor prognosis in AL amyloidosis and are routinely used to stage the disease and stratify treatment.85,86 The role of troponins in wild type TTR related amyloid (ATTR) is less well established but a recent study found levels TnI were higher in patients with ATTR amongst a heart failure with preserved ejection fraction (HFpEF) population.87

**Chagas cardiomyopathy**

Chronic Chagas disease, most prevalent in Latin America, is due to infection with Trypanosoma cruzi. There can be a long silent period before developing overt arrhythmia and heart failure symptoms. Cardiac Tn levels correlate with the severity of the cardiomyopathy and may be useful for monitoring chronic Chagas myocarditis, but are less sensitive than other biomarkers for predicting early disease development in seropositive individuals.92,93

**Peripartum cardiomyopathy**

Peripartum cardiomyopathy (PPCM) is a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within five months of delivery.88 In a prospective multi-centre study of 106 patients with newly diagnosed PPCM surviving over 6 months 31% patients had elevated TnI levels which negatively correlated with left ventricular ejection fraction (LVEF) at follow-up.89 Pre-eclamptic pregnant women have been reported to have elevated TnI levels.84 Although pre-eclampsia is associated with a higher incidence of PPCM no causal association has been shown.

**Future directions**

In many areas of cardiology risk scores are recommended in guidelines to facilitate the management of patients. For example, in acute coronary syndromes, troponin measurement is included in the GRACE (Global Registry of Acute Coronary Events) score.90 Even in individuals free of cardiovascular disease, the addition of TnI to the established ESC SCORE (Systematic COronary Risk Evaluation) has been shown to improve prediction of cardiovascular death and disease in the general population.91 In the cardiomyopathies, elevated Tn levels are almost invariably related to poor prognosis (Table 6). Several characteristics associated with its release in HCM indicate its inclusion in risk prediction models, such as HCM Risk-SCD,92 should be formally evaluated.

Although elevated Tn is recognised in children with cardiomyopathies there have been no systematic studies examining its role.90 There are few studies examining serial troponin measurement, which may be more cost-effective and time-efficient than, for example, repeated CMR imaging. And despite cardiac troponin gene mutations being a recognised as a cause of cardiomyopathy, it is not known whether genotype influences Tn detection in the circulation.

**Conclusions**

Cardiomyopathies need to be considered in the differential diagnosis of patients with elevated troponin, such as in those presenting with chest pain. Cardiac troponins correlate well with several important markers of disease severity and could be useful as a prognostic tool. There is currently insufficient evidence to support their role in routine management of all cardiomyopathies until we know that measurement may lead to clinical benefit and improved outcomes. High sensitivity assays offer an enormous opportunity to improve the detection and management of non-coronary disease and warrant further investigation in larger longitudinal studies.

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