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 sub-clinical 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 myofibrils.³ In 1963 Ebashi reported a new myofibrillar protein, troponin, which was the target for calcium.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 *TNNT2* in the atrium than in the ventricle, while the adult heart shows a greater expression of *TNNT2* 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.^{15,16} 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

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Key words: Troponin; biomarkers; cardiomyopathy.

Conflicts of interest: there are no conflicts of interest to declare.

Received for publication: 27 September 2016.
Revision received: 14 November 2016.
Accepted for publication: 8 December 2016.

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Cardiogenetics 2016; 6:6306
doi:10.4081/cardiogenetics.2016.6306

biomarkers such as creatine kinase MB.^{17,18} Mounting evidence led the European Society of Cardiology and American College of Cardiology to describe troponins as the *preferred marker* for myocyte 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.^{23,24}

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.

Table 1. Human troponin genes.

Gene name	Cytogenetic location	HGNC Symbol	HGNC Identifier	UniProt Identifier
Troponin T1, slow skeletal type	19q13.4	TNNT1	11948	P13805
Troponin T2, cardiac type	1q32	TNNT2*	11949	P45379
Troponin I1, slow skeletal type	1q31.3	TNNI1	11945	P19237
Troponin I2, fast skeletal type	11p15.5	TNNI2	11946	P48788
Troponin I3, cardiac type	19q13.4	TNNI3*	11947	P19429
Troponin C1, slow skeletal and cardiac type	3p21.1	TNNC1*	11943	P63316
Troponin C2, fast skeletal type	20q12-q13.11	TNNC2	11944	P02585

*Genes expressed in the heart.

Figure 1. Timeline illustrating the history of troponin, from its discovery to its modern-day use.

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}

Table 2. Troponin genes associated with familial cardiomyopathies.

Familial cardiomyopathy	TNNT2	TNNI3	TNNC1
Hypertrophic cardiomyopathy	✓	✓	✓
Dilated cardiomyopathy	✓	✓	✓
Restrictive cardiomyopathy	✓	✓	X
Non compaction cardiomyopathy	✓	X	X

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.³⁰ Levels are higher than in hypertension but lower in infiltrative conditions such as a amyloid.^{34,35}

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 assay³⁶ and up to 4% using a hs-Tn

assay.³⁷ Exercise can increase Tn levels.³⁸

Clinical correlates: troponin elevation in HCM is associated with greater LV wall thickness^{37,39-43} and LV mass.⁴⁴⁻⁴⁶ Two studies found Tn elevation in patients with LV outflow tract obstruction^{37,42} but another found no correlation.⁴⁰ The natural history of HCM includes progression to heart failure and Tn elevation is present in those with LV systolic dysfunction^{37,40,44} although the degree of hs-TnT elevation does not correlate linearly with ejection fraction.³¹ The relationship with New York Heart Association (NYHA) heart failure class however is conflicting.^{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^{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)^{40,42}. It is uncertain whether Tn can help detect the presence of paroxysmal atrial fibrillation (AF) with studies reporting both a positive^{40,47} and negative association.^{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.^{43,46,48,49} but data are conflicting on whether Tn measurement is an independent predictor of the extent of LGE.^{48,49} A high T2 signal on CMR, a potential marker of active tissue injury, in HCM is also associated with elevated troponin levels.⁵⁰

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.⁵¹ An adverse prognosis has also been demonstrated using a hs-TnT assay in two independent study cohorts.^{43,52}

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,^{44,46, 48,51,53} but was superior to hs-TnT at predicting which unaffected gene mutation carriers would go on to develop HCM.⁵⁴ To date there are few bio-

marker 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.³¹ It is a non-specific phenotype and the result of a wide range of cardiac insults.⁵⁵ Approximately half of cases are deemed to be idiopathic.⁵⁶ 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.⁵⁷ 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.⁵⁸⁻⁶¹ (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.^{27,62}

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.^{56,63,64} However, over 5 years of follow-up, elevated hs-TnT predicted a fall in LV ejection fraction.⁶⁵ As for LGE, an independent predictor of mortality in DCM,⁶⁶ only one study has investigated its relationship with Tn, finding that hs-TnT could predict LGE extent but TnT could not.⁶⁰ Elevated troponin levels and the presence of myocardial inflammation on CMR are predictors of LV recovery in children presenting with dilated cardiomyopathy.⁶⁷

Prognosis: The relationship between troponin and prognosis in DCM appears to depend on assay sensitivity. Four studies^{26, 28, 65, 68} found an association between TnT elevation and CV morbidity and mortality while three did not.^{60,69,70} Similarly, for TnI, three studies reported an association^{27,56,63} while two did not.^{65,69} Only hs-TnT has been found thus far to be an independent predictor of adverse cardio-

vascular events in all the studies that have examined it.^{60,65,70} 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.⁶³ The longest follow-up study over 5.1 years describes significantly more CV events in patients with elevated TnT or hs-TnT, but not TnI.⁶⁵

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.^{71,72}

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.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.⁷³

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.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.⁷⁴ 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.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 3. Troponin proteins expressed in the heart.

UniProt Identifier	Protein name	Protein Isoforms	Mass (kDa)	Function
P45379	Troponin T, cardiac	12	37	Binds troponin complex to tropomyosin
P19429	Troponin I, cardiac	1	22.5	Binds actin and inhibits actomyosin ATPase activity
P63316	Troponin C, cardiac and skeletal	1	18	Binds Ca ²⁺ to a low affinity Ca ²⁺ -specific binding site relieving the TnI inhibition

Table 4. Studies evaluating troponin in hypertrophic cardiomyopathy.

Year	1 st author	Biomarker	Population	Frequency of Tn elevation	Findings
2003	Sato	TnT	30 HCM	12/30 (40%)	12/30 patients with persistently elevated TnT levels had lower FS % and greater septal wall thickness, which thinned during follow-up (mean 21.5 months). 4/12 progressed to DCM (end stage dilated HCM)
2006	Pop	TnI TnT	7 HCM	3/7 (43%)	3/7 young adults with HCM had elevated TnI before exercise; 2 more had elevated TnI levels after exercise; only 1 had elevated TnT after exercise; all diminished using a β -blocker
2006	Taniguchi	TnT BNP	22 HCM	2/22 (9%)	Elevated TnT in 2/22 HCM patients with CHF. 3/16 (18%) had elevated TnT after mean 27.9 days of CHF treatment. Only 1 HCM patient had a CV event in 2 years of follow-up
2010	Kubo	TnI BNP	162 HCM		Higher in males, LVSD, AF; correlated with MWT, LVESD, E/Ea. Weak correlation with BNP. No correlation with NYHA or LVOTO
2010	Moreno	hs-TnT	95 HCM 45 Control	40/95 (42%) 2/45 (4.4%)	hsTnT was raised in patients in NYHA ≥ 3 , LVOTO, LVSD, abnormal BP response, LGE. hsTnT correlated with MWT, LA diameter and LVOT gradient
2011	Kubo	TnI, BNP	167 HCM	107/162 (66%)	Over 38.5 months of follow-up there were 20 CV deaths and 14 other CV events. The risk of events was 11.7 x higher if BNP and Trop were both high compared with both low
2013	Okamoto	hsTnT hsTnI BNP and CK	73 HCM	19/73 (26%) 0/73 (73%)	There was a correlation between absolute hsTnT and hsTnI levels and LV mass index, LVEDV, LVESV. hsTnI correlated with BNP. hsTnT inversely correlated with LVEF
2013	McGorrian	TnI hsTnI	19 definite HCM 24 borderline HCM 107 total	TnI 3/17 (18%) hsTnI 4/19 (21%)	107 previously un-investigated probands or relatives of HCM patients. Association between TnI and hsTnI and MWT. Those deemed to have borderline or definite HCM were more likely to have raised TnI or hsTnI
2013	Kawasaki	hs-TnT BNP and CK	53 HCM		hsTnT and BNP was higher in patients with LGE. hsTnT, BNP and combined were good for detecting LGE. LGE extent correlated with BNP but not hs-TnT. hsTnT levels correlated with fibrosis during 22 months follow-up
2013	Kubo	hs-TnT	183 HCM	99/183 (54%)	Over 4.1 ± 2.0 years of follow-up, 32% hsTnT +ve had CV events vs 7% of hsTnT -ve. CV event risk also increased with magnitude of hsTnT
2014	Jenab	hs-TnT	98 HCM	42/98 (43%)	Elevated hs-TnT was associated with age, chest pain, NYHA class, LVH, NVST, LAA, E/Ea, MWT, LVOT gradient; not with LVEF, AF, syncope, FH-SCD, LVOTO
2014	Cramer	hs-TnT	62 HCM	16/62 (26%)	Elevated hsTnT, correlated with LV mass and MWT
2014	Nakamura	hs-TnT, BNP	102 HCM	37/102 (36%)	37/102 (36%) had raised hsTnT, 24/97 (24%) had raised BNP. An elevated hs-TnT associated with AF, but not with any other echo variables (either as a continuous or a binary variable)
2015	Kubo	hs-TnT, BNP	35 HCM 8 amyloid 3 Fabry		hsTnT higher in infiltrative cardiomyopathy than HCM, BNP no different. hsTnT was the best differentiator between infiltrative and HCM
2015	Zhang	TnI, BNP	149 HCM	42/149 (28%)	TnI raised in 42/149 (28%). Associated with MWT, LV mass, frequency of enlarged LA, LVEDV, LVESV, BNP, reduced LVEF; but not with AF, FHSCD, syncope, NVST
2016	Hamada	TnT CK and LDH	77 HCM 14 HTN		12 control 3/77 (4%) Long-term follow-up study - 20 years. 3 (4%) of HCM patients had elevated TnT at baseline; 0 HTN or control patients did
2016	Zhang	TnI, BNP	163 HCM		Patients with LGE had higher TnI and BNP. LGE extent correlated with TnI and BNP. TnI & MWT independently predicted LGE presence; BNP did not
2016	Hasler	hsTnT	91 HCM	46/91 (51%)	Elevated hsTnT associated with higher MWT and LGE prevalence and worse exercise capacity. 15% of +ve hsTnT has adverse events vs 7% of -ve hsTnT. Timeline of hsTnT measurement and events not defined
2016	Ho	hsTnT BNP	38 HCM genes carriers without hypertrophy		Age 15.8 ± 8.6 . Median 2.9 years F/U. 4 developed HCM - higher BNP (but not hsTnT) at baseline. BNP and hsTnT increased during follow-up in those who developed HCM but decreased in those who did not

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; LVSD, left ventricular systolic dysfunction; LVESD, left ventricular end systolic diameter; LVEDV/LVESV, left ventricular end diastolic/systolic volume; LAA, left atrial area; NSVT, non sustained ventricular tachycardia; FHSCD, family history of sudden cardiac death; F/U, follow up.

fibrous tissue.³¹ 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.⁷⁶ 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 coro-

nary artery disease, postulating that Tn release may point toward a "hot" arrhythmic phase of the disease.⁷⁷⁻⁷⁹

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.³⁴ Early diagnosis is important because enzyme replacement therapy can halt disease progression.⁸⁰ A persistent increase in TnI was first reported in 3 out of 14 (21%) adults with AFD all of whom had LVH and LGE on CMR studies.⁸¹ A larger (n=62) study from the same centre

Table 5. Studies evaluating troponin in dilated cardiomyopathy. The study population is described as *acute* if patients were hospitalised and *chronic* if patients were stable and enrolled as outpatients.

Year	1 st author	Biomarker	Population	Frequency of Tn elevation	Findings
1997	Sato	TnT	17 acute	3/17 (18%)	3/17 (18%) +ve TnT. Cardiac event-free rate was significantly higher for TnT/Type III procollagen/7S collagen -ve. CK level similar
2001	Sato	TnT	60 chronic	27/60 (45%)	27/60 (45%) +ve TnT initially. 17/60 (28%) maintained +ve TnT after mean 16 mo of CHF treatment - their LVDd and LVEF worsened while they improved for the others; their cardiac event-free and survival rates were significantly worse.
2002	Soongswang	TnT	10 acute DCM 10 myocarditis 21 controls		10 paediatric DCM patients had identical mean TnT concentrations to 21 controls, and significantly less than 10 with myocarditis. CK-MB was similarly useful for differentiating between DCM and myocarditis
2004	Aso	TnT Tenascin-C	31 chronic	9/31 (29%)	TnT and Tenascin-C correlated
2005	Soongswang	TnT	19 acute		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)
2006	Nellessen	TnI	33 acute		TnI elevated in both idiopathic (n=33) and ischaemic (n=25) (> 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
2006	Taniguchi	TnT BNP	41 mixed	8/41 (20%)	Patients being investigated for CHF. 8/41 (20%) TnT +ve. 7/36 (19%) remained +ve after mean 38.7 days F/U. Significantly higher adverse CV event rates in TnT +ve (3/8 (38%) vs 5/33 (15%))
2007	Miller	TnT TnI BNP	13 chronic		All biomarkers significantly higher in ischaemic CM vs idiopathic DCM. Baseline TnT/TnI did not predict mortality
2008	Miettinen	TnI BNP	95 chronic	14/95 (15%)	14/95 (15%) TnI +ve. Consistent over mean 4.1 years F/U. LV dimension, volume and LVEF correlated with TnI level. Fewer end-points (CV death, transplant, ICD) if normal TnI
2011	Frankenstein	hsTnT	24 chronic	8/24 (33%)	8/24 (33%) +ve hsTnT (71% for IHD)/ No correlation with LVEF
2011	Kawahara	TnT hsTnT BNP	85 chronic	4/85 (5%)	46/85 (54%) 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
2013	Sramko	TnT, hsTnT BNP	27 chronic	7/27 (26%)	12/27 (44%) 7/27 (26%) TnT +ve, 12/27 (44%) hsTnT +ve. Across 42 patients with either idiopathic 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
2014	Li	TnI CK-MB	310 acute	64/310 (21%)	64/310 (21%) +ve TnI - larger LVDd/LA/RV diameters, but not LVEF 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
2014	Bakal	hsTnT BNP	27 chronic		hsTnT higher in ischaemic CM than DCM, BNP was not different
2015	Baba	TnI TnT hsTnT BNP	54 chronic	15/54 (28%) 8/54 (15%) 17/54 (31%)	17/54 (31%) +ve hsTnT, 8/54 (15%) +ve TnT, 15/54 (28%) +ve TnI. During mean 5.1 years F/U, +ve TnT or hsTnT had significantly more CV events than -ve. +ve TnI did not. Only +ve hsTnT was an independent predictor of all CV events. CV events varied with hsTnT levels also. LVDd, LVDs and LVEF were similar at baseline between hsTnT +ve and -ve, but significantly different (worse in +ve) after F/U
2015	Raimondi	TnI	66 acute	35/66 (53%)	Children followed for 2.2 years. TnI and inflammation on CMR predicts LV recovery

CHF, congestive heart failure; CM, cardiomyopathy; DCM, dilated cardiomyopathy; LVDd LV, diastolic diameter; LVEF, left ventricular ejection fraction. CK, creatine kinase; CK-MB, creatine kinase MB isoform; 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.

	Prevalence % Median (range)	Diagnosis	Staging	Prognosis
Hypertrophic cardiomyopathy	36 (4-66)		✓	✓
Dilated cardiomyopathy	27 (5-54)		✓	✓
Restrictive cardiomyopathy	-			
Left ventricular non-compaction	17			✓
Arrhythmogenic right ventricular cardiomyopathy	-			
Anderson Fabry disease	37 (21-40)		✓	
Takotsubo cardiomyopathy	87			✓
Amyloid	-		✓	✓
Chagas cardiomyopathy	-	✓	✓	
Peripartum cardiomyopathy	31			

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-TnT 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 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 discriminate between these two disorders at presentation.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.⁸⁷

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.⁸⁸ Elevated cardiac Tn levels are associated with a poor prognosis in

AL amyloidosis and are routinely used to stage the disease and stratify treatment.^{89,90} 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.⁹¹

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.⁹⁴ In a prospective multi-centre study of 106 patients with newly diagnosed PPCM surviving over 6 months 31% patients had elevated TnT levels which negatively correlated with left ventricular ejection fraction (LVEF) at follow-up.⁹⁵ Pre-eclamptic pregnant women have been reported to have elevated TnI levels.⁹⁶ 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.⁹⁷ 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.⁹⁸ 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,⁹⁹ should be formally evaluated.

Although elevated Tn is recognised in children with cardiomyopathies there have been no systematic studies examining its role.¹⁰⁰ 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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