Original research article

A prospective study on high sensitive cardiac troponin in cardiac patients in Karnataka region

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Abstract

Introduction: The troponin complex regulates the contraction of striated muscles and consists of three subunits (troponin C, troponin T, and troponin I). Troponin C is a 18 ku protein that binds to calcium ions. Troponin T is a 37 ku protein that binds to tropomyosin, thereby attaching the troponin complex to the thin filament. Troponin I is a 24 ku protein that binds to actin and decreases troponin C affinity for calcium, thus inhibiting actin–myosin interactions.

Material and Methods: We included 4748 consecutive patients who presented to the General medicine Department and casualty with suspected acute coronary syndrome to the M.R. Medical College and Basaveshwar Hospital, kalaburagi between 1 June 1999 and December 2001. All patients who had cardiac troponin requested by the attending clinician for suspected acute coronary syndrome were included.

Results: There were 4870 patients with suspected acute coronary syndrome (mean age 61 ± 16 years, 57% men). The median cardiac troponin concentration was 5 ng/L (interquartile range 2–22 ng/L). There were 1151 (24%) patients with cardiac troponin concentrations above the URL (Group 5); 723 (15.2%) patients were classified as having type 1 myocardial infarction, 158 (3.3%) type 2 myocardial infarction, and 270 (5.7%) with myocardial injury.

Conclusion: High-sensitivity cardiac troponin I is an excellent predictor of heart failure hospitalizations and cardiac death in patients with suspected acute coronary syndrome. Troponin concentrations may, in particular, be used to identify patients without myocardial infarction who are at risk of heart failure.

Key words: High-sensitivity cardiac troponin, acute coronary syndrome, Heart failure

Introduction

The troponin complex regulates the contraction of striated muscles and consists of three subunits (troponin C, troponin T, and troponin I). Troponin C is a 18 ku protein that binds to calcium ions. Troponin T is a 37 ku protein that binds to tropomyosin, thereby attaching the troponin complex to the thin filament. Troponin I is a 24 ku protein that binds to actin and decreases troponin C affinity for calcium, thus inhibiting actin–myosin interactions.[1]Troponin T and troponin I are present in cardiac and skeletal muscles, but are encoded by different genes in the two types of muscle, yielding proteins that are immunologically distinct.[1] Assays that are based on high-affinity antibodies and are specific

for cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are available. Because the amino acid sequence of cardiac troponin C and skeletal troponin C is identical, no such assays have been developed for the troponin C component.

The majority of cardiac troponin (cTn) is bound to myofilaments, and the remainder is free in the cytosol which accounts for 3%–8% of the total amount.[2] After disruption of the sarcolemmal membrane of the cardiomyocyte, troponin from the cytoplasmic pool is initially released, followed by a more protracted release from quantities bound to deteriorating myofilaments.[1] In peripheral blood, cTnT begins to rise within three to four hours after the onset of myocardial injury and remains increased for 10–14 days.[3]

Material and Methods:

We included 4748 consecutive patients who presented to the General medicine Department and casualty with suspected acute coronary syndrome to the M.R.Medical college and Basaveshwar Hospital , kalaburagi between 1 June 1999 and December 2001. All patients who had cardiac troponin requested by the attending clinician for suspected acute coronary syndrome were included.

Statistical analysis

We established the negative predictive values for the primary outcome across a range of troponin concentrations starting at 1 ng/L. Patients with ST-segment elevation myocardial infarction and troponin concentrations above the 99th centile on presentation were not included in this analysis. Previous analyses of high-sensitivity cardiac troponin T assay have used a threshold based on the lowest detectable concentration. However, the precision of the high-sensitivity cardiac troponin I assay at low concentrations is sufficient to enable the assessment of a range of thresholds.[4,5,6,7,8,9,] As such, we selected a threshold on the basis of clinical need rather than assay performance. The trial steering committee prespecified that the cardiac troponin threshold on presentation should achieve a negative predictive value of at least 99·5% for the primary outcome. In sample size calculations, we estimated that 3500 patients would enable us to estimate a negative predictive value of 99·5% with a 95% CI of 99·2–99·7, and that we had 92% power for an α of 0·05 to test the null hypothesis that the negative predictive value was less than 99%.

Result

Table 1: Baseline characteristics of patients with suspected acute coronary syndrome stratified by cardiac troponin concentration

	Patients stratified by peak troponin concentration				
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**[a]
	***n* = 900 (19%)**	***n* = 899 (19%)**	***n* = 899 (19%)**	***n* = 899 (19%)**	***n* = 1151 (24%)**
Troponin, ng/L (median, range)					
Men	1.9 (1.2–2.0)	3.0 (2.1–4.0)	5.9 (4.1–8.0)	15.0 (8.1–34.0)	484.5 (34.1–50 000)
Women	1.2 (1.2–1.9)	2.0 (2.0–2.9)	3.0 (3.0–6.0)	9.0 (6.1–16.0)	100.0 (16.1–50 000)
Age, years (mean, SD)	49 (13)	58 (14)	66 (14)	71 (14)	71 (15)
Females	378 (42%)	378 (42%)	378 (42%)	378 (42%)	545 (47%)
Diabetes mellitus	68 (9%)	115 (15%)	130 (16%)	162 (21%)	191 (18%)
Hypertension	120 (16%)	224 (29%)	290 (36%)	316 (40%)	444 (41%)
Hyperlipidaemia	119 (16%)	209 (27%)	223 (28%)	238 (30%)	336 (31%)

Ischaemic heart disease	93 (12%)	201 (26%)	304 (38%)	372 (47%)	409 (38%)
Previous myocardial infarction	58 (6%)	120 (13%)	159 (18%)	209 (23%)	244 (21%)
Previous stroke	27 (3%)	48 (5%)	54 (6%)	90 (10%)	107 (9%)
Heart failure at index presentation	0 (0%)	7 (1%)	21 (2%)	83 (9%)	243 (21%)
Current or ex-smoker	315 (57%)	309 (58%)	287 (56%)	252 (59%)	401 (63%)
Admission ACE inhibitor/ARB	88 (16%)	160 (28%)	209 (36%)	221 (42%)	270 (38%)
Admission beta blocker	65 (12%)	108 (19%)	166 (29%)	189 (36%)	236 (33%)
Killip class					
1	784 (99%)	784 (97%)	786 (96%)	699 (88%)	923 (85%)
2	8 (1%)	25 (3%)	30 (4%)	84 (11%)	108 (10%)
3	0	0	0 (0%)	14 (2%)	52 (5%)
4	0	0	0	1 (0%)	3 (0%)
Creatinine, mg/dL (mean, SD)	0.84 (0.14)	0.86 (0.21)	0.91 (0.26)	1.07 (0.63)	1.13 (0.75)
Heart rate, b.p.m. (mean, SD)	79 (18)	78 (20)	78 (20)	83 (24)	86 (29)
Systolic blood pressure, mmHg (mean, SD)	136 (21)	139 (25)	138 (23)	140 (28)	139 (30)

Values are numbers (proportion), except where indicated.
SD, standard deviation; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
[a]Group 5—all patients with cardiac troponin concentrations >upper reference limit.

Table 2: Heart failure hospitalization or cardiac death in suspected acute coronary syndrome stratified by troponin concentration

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**All patients**
	***n* = 900 (19%)**	***n* = 899 (19%)**	***n* = 899 (19%)**	***n* = 899 (19%)**	***n* = 1151 (24%)**	***n* = 4748 (100%)**
Troponin (ng/L): Men	1.2–2.0	2.1–4.0	4.1–8.0	8.1–34.0	34.1–50 000	1.2–50 000
Troponin (ng/L): Women	1.2–1.9	2.0–2.9	3.0–6.0	6.1–16.0	16.1–50 000	1.2–50 000
Heart failure hospitalization						
Events, *n*	0	2	4	21	56	83
Person years	407	410	390	390	473	2071
Incidence (per 1000 person years)	0	5	10	54	118	40
HR, unadjusted	1		4.1	21.8	47.2	
HR, model 1	1		2.4	9.9	21.4	
HR, model 2	1		3.0	11.7	28.9	
HR, model 1, continuous[a]	2.80 (1.81–4.31)				1.03 (0.96–1.12)	
Heart failure hospitalization or cardiac death						

Events, *n*	0	2	5	29	84	120
Person years	407	410	390	390	473	2071
Incidence (per 1000 person years)	0	5	13	74	178	58
HR, unadjusted	1		5.2	30.2	71.3	
HR, model 1	1		2.7	11.6	27.6	
HR, model 2	1		2.7	14.4	34.1	
HR, model 1, continuous[a]	3.03 (2.05–4.48)				1.03 (0.97–1.10)	

Hazard ratio (95% CI). Model 1 adjusts for age and sex; model 2 additionally adjusts for diabetes mellitus, hypertension, and ischaemic heart disease, previous myocardial infarction, systolic blood pressure at the index presentation, creatinine at the index presentation and an interaction term between ischaemic heart disease and previous myocardial infarction.
HR: hazard ratio.
[a]Analysis of troponin as a continuous variable among patients with troponin levels below the upper reference limit (Groups 1–4) and above the upper reference limit (Group 5).

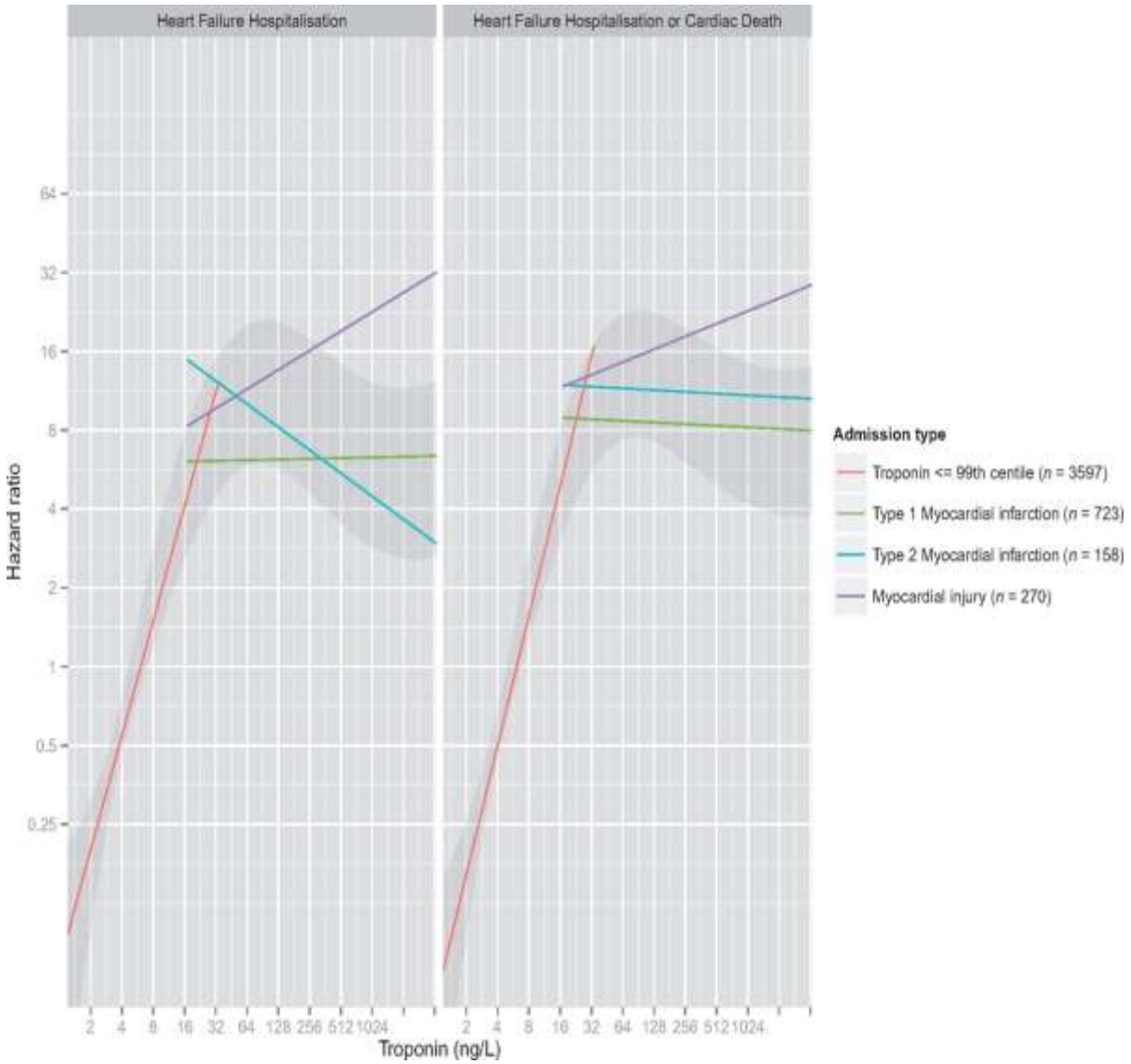

Figure 1:

Association between peak cardiac troponin concentration and time to first event for heart failure hospitalization, and heart failure hospitalization or cardiac death. Departures from linearity were explored using penalized spline smoothing functions (grey band). The association was also analysed after stratifying patients into those with a peak troponin concentration less than the upper reference limit (URL) (red line), and those with troponin concentrations above the URL, with a specific index diagnosis (type 1 myocardial infarction, green line; type 2 myocardial infarction, blue; myocardial injury, purple).

Discussion

In consecutive patients with suspected acute coronary syndrome high-sensitivity cardiac troponin I concentrations predict an increased risk of subsequent hospitalization with heart failure or cardiac death. Interestingly the relationship between cardiac troponin concentration and heart failure was strongest for patients without myocardial infarction. In these patients, the risk of subsequent hospitalization increased three-fold for every doubling in cardiac troponin concentration and the addition of troponin to a model with clinical features and cardiovascular risk factors markedly improved discrimination.Heart failure may occur following myocardial infarction in patients with significant myocardial injury and left ventricular systolic impairment. Our observations from a large cohort of consecutive patients with suspected acute coronary syndrome demonstrate that any increase in cardiac troponin concentration <99th centile is associated with an increase in the risk of developing heart failure. Interestingly, in patients with cardiac troponin concentrations >99th centile, further increases in cardiac troponin did not identify those at higher risk. This was true even among patients with type 1 myocardial infarction in whom one might expect more extensive myocardial injury to be associated with a greater risk of heart failure. we have defined a cardiac troponin threshold at presentation that identifies almost two-thirds of patients as being at very low risk of myocardial infarction or cardiac death, and who could potentially be safely discharged from the emergency department. Implementation of this approach would reduce avoidable hospital admission and have major benefits for both patients and health-care providers. Our observations complement previous studies of the use of cardiac troponins to triage patients with suspected acute coronary syndrome in emergency departments. The limit of detection and the limit of blank of a high-sensitivity cardiac troponin T assay both show promise for the assessment of patients at presentation.[10, 11, 12] These studies were included in a systematic review and meta-analysis[5] showing that cardiac troponin T concentrations below the limit of detection had a false negative rate of 1·5% and identified 25% of patients as low risk. However, half of the studies used a contemporary troponin assay as a reference and would have missed smaller myocardial infarctions that could only be detected with a high-sensitivity assay, which will inflate the negative predictive value. In our analysis, we judged the final diagnosis using a high-sensitivity assay to ensure robust case ascertainment. Unlike previous studies of the cardiac troponin T assay, our analysis was the first to use a high-sensitivity cardiac troponin I assay, which has greater precision and reproducibility at low concentrations and at the proposed threshold. This will ensure the application of this approach is consistent across sites, analysers, and reagent batches: a prerequisite for use in clinical practice. Furthermore, use of cardiac troponin I at our threshold identifies two-to-three-times more low-risk patients than do previous approaches,[10, 11, 12, 13] which would avoid the need for repeat testing in most patients, or the incorporation of clinical risk scores used in accelerated diagnostic pathways.[14,15,16] Studies are needed assess the clinical and cost-effectiveness of our approach in routine clinical practice.

Conclusion

High-sensitivity cardiac troponin I is an excellent predictor of heart failure hospitalizations and cardiac death in patients with suspected acute coronary syndrome. Troponin concentrations may, in particular, be used to identify patients without myocardial infarction who are at risk of heart failure. HscTn assays will help triage patients with ACS more accurately and rapidly than prior assays. They will also improve risk stratifications of patients presenting with chest pain. It may be that this group of patients will benefit from N-terminal pro-BNP testing and/or echocardiography. Intervention studies, ideally randomized clinical trials, are needed to determine whether the costs of such a strategy are justified by benefits such as reducing or delaying heart failure admissions

References

1. Antman EM. Decision making with cardiac troponin tests. *N Engl J Med.* 2002;346:2079–2082.
2. Katus HA, Remppis A, Scheffold T, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol.* 1991;67:1360–1367.
3. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation.* 2007;115:e356–e375.
4. Thygesen K, Alpert JS, Jaffe AS. Third universal definition of myocardial infarction. *Circulation.* 2012;**126**:2020–2035.
5. Mills NL, Churchhouse AM, Lee KK. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA.* 2011;**305**:1210–1216
6. Shah AS, Griffiths M, Lee KK. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ.* 2015;**350**:g7873.
7. Body R, Carley S, McDowell G. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol.* 2011;**58**:1332–1339.
8. Rubini Gimenez M, Hoeller R, Reichlin T. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. *Int J Cardiol.* 2013;**168**:3896–3901.
9. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol.* 2014;**63**:2569–2578.
10. Thygesen K, Alpert JS, Jaffe AS. Third universal definition of myocardial infarction. *Circulation.* 2012;**126**:2020–2035.
11. Mills NL, Churchhouse AM, Lee KK. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA.* 2011;**305**:1210–1216.
12. Shah AS, Griffiths M, Lee KK. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ.* 2015;**350**:g7873.
13. Body R, Burrows G, Carley S. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. *Clin Chem.* 2015;**61**:983–989.
14. Than M, Cullen L, Aldous S. 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the

ADAPT trial. *J Am Coll Cardiol.* 2012;**59**:2091–2098.
15. Carlton EW, Cullen L, Than M, Gamble J, Khattab A, Greaves K. A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. *Heart.* 2015;**101**:1041–1046
16. Cullen L, Mueller C, Parsonage WA. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol.* 2011;**62**:1242–1249.