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ORIGINAL RESEARCH ARTICLE

Mild troponin I elevation does not predict ischemia on myocardial perfusion imaging

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ABSTRACT

Introduction: Data are limited on the degree of mild troponin I elevation and clinical risk factors in predicting myocardial ischemia.

Methods: Hospitalized adult patients who underwent myocardial perfusion imaging (MPI) from 2015 to 2016 at Rochester General Hospital and had mild troponin I elevation (>0.1 and <1.5 ng/mL) were included. Predictors of outcomes were determined using logistic regression model.

Results: One hundred and sixty-six patients with mild troponin I elevation who underwent MPI were followed. Mean age was 69.6 ± 12.5 years and 53.0% of the patients were female. Fourteen patients (8.4%) presented with typical chest pain (CP), 60 patients (36.1%) had atypical CP and 92 patients (55.4%) had no CP on presentation. MPI was positive for ischemia in 45 patients (27.1%). There was no difference in peak troponin I level with ischemia versus no ischemia on MPI (0.34 ng/dL [0.13-0.69] vs. 0.23 ng/dL [0.14-0.50], p value 0.254). Atypical CP did not predict the presence of ischemia on MPI (odds ratio [OR] 1.97, 95% confidence interval [CI] 0.91-4.26). Coronary artery disease (CAD) history (age and sex adjusted p value 0.013), diabetes (adjusted p value 0.036), creatinine ≥2 mg/dL (adjusted p value 0.019) and dialysis (adjusted p value 0.006) were statistically significant predictors of ischemia on MPI.

Conclusions: In patients presenting with mild troponin I elevation, peak troponin I level did not predict ischemia on MPI. The presence of CAD history, diabetes, elevated creatinine and dialysis were predictors of ischemia on MPI.

Keywords: Myocardial perfusion imaging, Risk factors, Troponin I

Introduction

Troponin I elevation is a sensitive marker for the detection of myocardial injury. In patients presenting with symptoms of myocardial ischemia, troponin elevation is very helpful for the diagnosis of acute myocardial infarction. A negative troponin level has significant negative predictive value (1). However, the interpretation of troponin I elevation in patients with atypical chest pain, non-cardiac chest pain and no chest pain is particularly challenging. Elevated troponin I is commonly seen in the absence of coronary artery disease (CAD), such as in critically ill patients, stroke or subarachnoid hemorrhage, coronary vasospasm, rhabdomyolysis, pulmonary embolism, renal failure, burns and infiltrative diseases like amyloidosis and sarcoidosis (2). However, patients with critical CAD who present with demand mediated ischemia as a result of the physiological stress from another acute medical illness is also commonly a cause for elevated troponin.

A recent study published in *American Journal of Emergency Medicine* in 2015 reported a significant difference in the mean level of troponin I between patients diagnosed with ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and non-cardiac causes, which were 10.2, 0.4 and 0.14 ng/mL, respectively (2). Patient who present with mild troponin elevation, without a clinical diagnosis of myocardial infarction, typically undergo further non-invasive cardiac evaluation for the presence of obstructive CAD. Data are limited on whether mild troponin elevation predicts the presence of significant myocardial ischemia due to CAD. In this study, we examine the clinical value of mild troponin elevation in predicting the presence of myocardial ischemia by myocardial perfusion imaging (MPI).

Method

Study population

This is a retrospective observational study. All patients admitted to Rochester General Hospital (RGH) aged >= 18 years who underwent MPI between March 2015 and February 2016 were included. Troponin I level in RGH was measured

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using the ADVIA Centaur TnI-Ultra assay. This is a three-site sandwich immunoassay using direct chemiluminometric technology. The ADVIA Centaur instrument in RGH underwent 2-point calibration every 28 days. The assay range was 0.006-50 ng/mL and the normal range was 0.00-0.09 ng/mL. Hemolysis (<500 mg/dL hemoglobin), lipemia (<1000 mg/dL triglycerides) and icterus (<20 mg/dL bilirubin) have an insignificant effect on the assay.

Patients with a mildly elevated troponin level within the range of 0.1 ng/mL to 1.5 ng/mL were identified. Clinical data collection was performed and examined independently by two different physicians. Data regarding demographic variables, past medical history (PMH), medications, laboratory data, clinical symptoms and hospital course were collected. All troponin levels during the hospital course for each patient were recorded and the peak troponin level prior to MPI was used for analysis.

Myocardial perfusion imaging (MPI)

All patients underwent exercise or pharmacological MPI. The results reported from the MPI study were used to classify patients with low risk and high risk for myocardial ischemia. Low-risk MPI was defined as either (i) no ischemia, (ii) minimal or small area of ischemia or (iii) strong suspicion for artifacts. High-risk MPI was identified as moderate-to-severe reversible ischemia in a moderate-to-large area.

Coronary angiography and revascularization

Results of coronary angiography were obtained from the cardiac catheterization laboratory database. Obstructive CAD was defined by angiography as a left main stenosis ≥50% or a stenosis ≥70% in any other major artery or branch vessel.

Statistical analysis

Statistical analyses were performed suing SPSS® Statistics 20. Quantitative data were described using mean (M) and standard deviation (SD). Qualitative data were described using number and percentage. Since the distribution of troponin I level was right-skewed, median (lower quartile [Q1]-higher quartile [Q3]) was used to describe this set of values. Association with the outcome was tested using independent t-test, in case of quantitative variables, and using chi-square test, in case of qualitative variables. The strength of the association was estimated using age and sex-adjusted odds ratio (OR) with 95% confidence interval (CI). Logistic regression was used to determine independent predictors of the outcome. The contribution of the individual predictor in the logistic regression model was assessed using adjusted p value and adjusted OR. Adjusted OR indicates the change in odds resulting from a unit change in the predictor adjusted for other covariates in the model. Significance of the obtained results was judged at the 5% level. It is quoted as two-tailed probabilities.

Results

Over a one-year period from March 2015 to February 2016, 1343 patients who presented to the emergency room at Rochester General Hospital underwent MPI. One hundred and sixty-six patients met the inclusion criteria of mildly elevated troponin I (Fig. 1). Baseline characteristics of these patients were summarized in Table I. Mean age was 69 ± 12 years and 47% were men. Median initial troponin level was 0.16 ng/dL (0.1-0.33) and the median peak troponin I level was 0.26 ng/dL (0.14-0.54). Presenting symptoms included typical chest pain (8.4%), atypical chest pain (36.1%) and no chest pain (55.5%). Co-morbidities included hypertension (88.0%), CAD history (59.0%), diabetes (52.4%), dialysis (15.7%) and prior revascularization (37.4%).

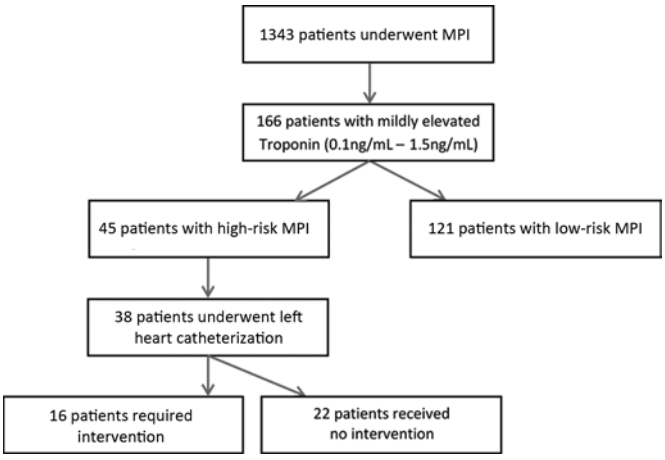

Fig. 1 - Flow chart of patient selection in the study.

MPI was low risk in 121 patients (72.9%). Of these, 105 patients (86.8%) had no ischemia and the remainder (23.2%) had mild ischemia. Forty-five patients (27.1%) had high-risk MPI. Table II shows the comparison of demographics between the low-risk versus the high-risk MPI groups. There was no significant difference in terms of age, sex, BMI and ethnicity between the low-risk versus the high-risk MPI groups. Table II also shows the comparison of troponin. Initial mean troponin I levels were significantly lower in patients with low-risk versus high-risk MPI (0.15 ng/dL [0.1-0.31] vs. 0.23 ng/dL [0.12-0.44], p = 0.032). Peak troponin I values did not differ significantly in the two groups (0.23 ng/dL [0.14-0.50] vs. 0.34 ng/dl [0.13-0.69], p = 0.254). There was no statistically significant difference in the predictive values of elevated troponin for high-risk MPI across gender (p value 0.955) or ethnicity (p value 0.307) (Supplementary Tab. I, available online as Supplementary material at www.heart-int.com).

Table II shows the comparison of clinical variables between the low-risk versus high-risk MPI groups. Compared to patients with low-risk MPI, patients with high-risk MPI were more likely to have typical chest pain (age and sex adjusted p value 0.004), CAD (adjusted p value 0.013), diastolic congestive heart failure (CHF) (adjusted p value 0.049), coronary artery bypass graft surgery (CABG) (adjusted p value 0.004), dialysis (adjusted p value 0.006) and diabetes (adjusted p value 0.036). Aspirin and dual anti-platelet use were significantly greater in high-risk MPI compared to low-risk (adjusted p value 0.027 and adjusted p value 0.005, consecutively). Additionally, patients with high-risk MPI were more likely to

TABLE I - Baseline characteristics of the study population

Baseline characteristics	n = 166
Male n (%)	78 (46.9)
Age M ± SD	69 ± 12
BMI M ± SD	30.2 ± 6.8
Ethnicity n (%)	
White	86 (51.8)
African American	55 (33.1)
Hispanic	12 (7.2)
Asian	4 (2.4)
Unknown	9 (5.4)
Co-morbidities n (%)	
CAD	98 (59.0)
Systolic CHF	43 (25.9)
Diastolic CHF	52 (31.3)
Stent	36 (21.7)
CABG	26 (15.7)
Atrial fibrillation	49 (29.5)
Family history	85 (51.2)
CVA	40 (24.1)
Hypertension	146 (88.0)
OSA	18 (10.8)
PVD	17 (10.2)
COPD	36 (21.7)
Dialysis	26 (15.7)
Hypercholesterolemia	109 (65.7)
Diabetes	87 (52.4)
Malignancy	40 (24.1)
Medication n (%)	
Beta-blocker	136 (81.9)
Calcium channel blocker	66 (39.8)
Statin	137 (82.5)
Aspirin	122 (73.5)
Diuretics	93 (56.0)
Anti-platelets (clopidogrel/ticagrelor)	34 (20.5)
ACE-I/ARB	80 (48.2)
Nitrates	63 (38.0)
Presentation n (%)	
Typical chest pain	14 (8.4)
Atypical chest pain	60 (36.1)
No chest pain	92 (55.5)

ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blockers; BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebro-vascular accident; M = mean; OSA = obstructive sleep apnea; PVD = peripheral vascular disease; SD = standard deviation.

have left ventricular hypertrophy (LVH) on echocardiogram (adjusted p value 0.012) and higher serum creatinine level (adjusted p value 0.019) (Supplementary Fig. 1, available online as Supplementary material at www.heart-int.com).

Table III shows the multivariate regression analysis. After adjusting for co-variables, predictors of high-risk MPI was the presence of CAD (adjusted OR 2.22, 95% CI 1.0-4.7, p value 0.047), serum creatinine >2 mg/dL (adjusted OR 2.36, 95% CI 1.1-5.1, p value 0.028), dialysis (adjusted OR 3.1, 95%CI 1.3-7.4, p value 0.025), diabetes (adjusted OR 2.3, 95% CI 1.1-4.9), antiplatelet use (adjusted OR 3.2, 95% CI 1.4-7.4, p value 0.005). There was no statistically significant association between elevated troponin I with high-risk MPI in any of the multivariate regression models (Tab. III).

No patient with low-risk MPI underwent further evaluation with angiogram. Thirty-eight of the 45 patients (84.4%) with high-risk MPI underwent left heart catheterization. Seven patients (15.6%) did not proceed with angiogram due to either increased risk of contrast-induced nephropathy, critical illness or personal preference. Twenty-one of 38 patients (55.3%) did not receive any intervention during angiogram due to normal coronary arteries, non-obstructive CAD or due to chronic diffuse CAD not amenable to revascularization. Seven patients (18.4%) had chronic total occlusion that was not considered the culprit lesion. Sixteen patients (42.0%) underwent revascularization: 11 patients underwent percutaneous coronary intervention (PCI) and 5 patients underwent CABG.

Discussion

Troponin I is a sensitive marker of myocardial infarction and is one of the most commonly ordered laboratory tests in patients presenting with a suspicion of myocardial ischemia (3). The independent prognostic value of troponin elevation for 30-day mortality in patients with acute myocardial ischemia has been previously reported (4). However, the elevation of troponin I is not always indicative of acute coronary syndrome. A study of 615 patients presenting with elevated troponin T level reported that only 53% were diagnosed with acute coronary syndrome. The remaining patients were diagnosed with other etiologies including arrhythmia, myocarditis, sepsis, pulmonary disease, intracranial hemorrhage, stroke and surgical disorder. Hypertension, history of CAD and a higher troponin T level were independent predictors of myocardial ischemia (5). Previous studies have concluded that higher level of troponin elevation is predictive of myocardial ischemia related to acute coronary syndrome, while atypical chest pain and non-cardiac chest pain were associated with lower levels of troponin elevation. However, the data on the predictive value of mild troponin elevation in detecting myocardial ischemia and critical CAD are not well studied.

MPI is a useful non-invasive imaging modality to evaluate the presence of ischemia in patients with moderate risk for CAD. MPI is often used for risk stratification in patients with indeterminate and mild troponin elevation. Subsequently, patients with MPI positive for ischemia, may undergo further invasive testing with angiography.

We designed this study to determine the predictive value of mild troponin elevation (0.1 ng/mL to 1.5 ng/mL) in predicting the presence of myocardial ischemia on MPI. Our study demonstrated that 8.1% of patients with typical chest pain underwent MPI, while a majority had no chest pain (36.4%) or atypical chest pain (55.5%). About one-quarter of

TABLE II - Comparison of baseline characteristics and clinical variables between patients with low-risk versus high-risk MPI

Baseline characteristics		Outcome				(Adjusted p value)[a]
		Low-risk (n = 121)		High-risk (n = 45)		
Male	n (%)	55	(45.4)	23	(51.1)	(0.507)
Age	M ± SD	70 ± 12		68 ± 13		(0.344)
BMI	M ± SD	30 ± 7		30 ± 7		(0.879)
Ethnicity	n (%)					
White		62	(51.2)	24	(53.3)	(0.702)
African American		38	(31.4)	17	(37.7)	
Hispanic		10	(8.2)	2	(4.4)	
Asian		3	(2.4)	1	(2.2)	
Unknown		8	(6.6)	1	(2.2)	
Troponin level						
Admission	Median (Q1-Q3)	0.15 (0.1-0.31)		0.23 (0.12-0.44)		(0.032)
Peak	Median (Q1-Q3)	0.23 (0.14-0.50)		0.34 (0.13-0.69)		(0.254)
Presentation	n (%)					
Typical chest pain*	5	(4.1)	9	(20.0)		(0.004)*
Atypical chest pain	41	(33.8)	19	(42.2)		
No chest pain	75	(61.9)	17	(37.7)		
Smoking	n (%)					
Non-smoker		41	(33.8)	15	(33.3)	(0.349)
Former smoker		59	(48.7)	17	(37.7)	
Smoker		21	(17.3)	13	(28.8)	
Co-morbidities	n (%)					
CAD*		65	(53.7)	33	(73.3)	(0.013)*
Systolic CHF		32	(26.4)	11	(24.4)	(0.592)
Diastolic CHF*		33	(27.2)	19	(42.2)	(0.049)*
Stent		22	(18.1)	14	(31.1)	(0.090)
CABG*		13	(10.7)	13	(28.8)	(0.004)*
Atrial fibrillation		36	(29.7)	13	(28.8)	(0.808)
Family history		61	(50.4)	24	(53.3)	(0.681)
CVA		29	(23.9)	11	(24.4)	(0.906)
Hypertension		103	(85.1)	43	(95.5)	(0.084)
OSA		13	(10.7)	5	(11.1)	(0.887)
PVD		10	(8.2)	7	(15.5)	(0.171)
COPD		24	(19.8)	12	(26.6)	(0.387)
Dialysis*		13	(10.7)	13	(28.8)	(0.006)*
Hypercholesterolemia		78	(64.4)	31	(68.8)	(0.543)
Diabetes*		57	(47.1)	30	(66.6)	(0.036)*
Malignancy		30	(24.7)	10	(22.2)	(0.873)
Medication	n (%)					
Beta blocker		98	(80.9)	38	(84.4)	(0.573)
Statin		99	(81.8)	38	(84.4)	(0.701)
Aspirin*		83	(68.5)	39	(86.6)	(0.027)*
Anti-platelet*		18	(14.8)	16	(35.5)	(0.005)*
ACE-I/ARB		62	(51.2)	18	(40.0)	(0.134)
Nitrates		42	(34.7)	21	(46.6)	(0.158)

To be continued

TABLE II - Continued

Baseline characteristics		Outcome				(Adjusted p value)[a]
		Low-risk (n = 121)		High-risk (n = 45)		
Investigation	n (%)					
BNP (>100 pg/mL)		60	(49.5)	26	(57.7)	(0.235)
Cr (≥2 mg/dL)*		25	(20.6)	18	(40.0)	(0.019)*
BUN (>20 mg/dL)		68	(56.1)	31	(68.8)	(0.092)
Anemia		61	(50.4)	26	(57.7)	(0.391)
BBB on ECG		17	(14.0)	11	(24.4)	(0.079)
LVH on ECG		16	(13.2)	4	(8.8)	(0.380)
ST-T change on ECG		43	(35.5)	21	(46.6)	(0.193)
EF <35% on Echo		20	(16.5)	5	(11.1)	(0.232)
LVH on Echo*		53	(43.8)	30	(66.6)	(0.012)*

ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blockers; BBB = bundle branch block; BMI = body mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebro-vascular accident; ECG = electrocardiogram; EF = ejection fraction; LVH = left ventricular hypertrophy; M = mean; MPI = myocardial perfusion imaging; OSA = obstructive sleep apnea; PVD = peripheral vascular disease; Q1-Q3 = lower quartile – higher quartile; SD = standard deviation.
[a] p value adjusted for age and gender.
* Statistically significant adjusted p value between the high-risk and low-risk groups.

TABLE III - Independent predictors of high-risk MPI in multivariate analysis

	OR	95% CI	p value	Comment
Diabetes*	2.3	1.1-4.9	0.030	Adjusted for anti-platelet and LVH
Anti-platelet*	3.2	1.4-7.4	0.005	Adjusted for diabetes and LVH
Dialysis*	3.1	1.3-7.4	0.025	Adjusted for CAD
CAD*	2.2	1.0-4.7	0.047	Adjusted for dialysis
Cr ≥2*	2.36	1.1-5.1	0.028	Adjusted for diabetes and CAD
Elevated Troponin I	1.8	0.6-5.3	0.303	Adjusted for CAD and diabetes
	1.5	0.5-4.5	0.469	Adjusted for Cr ≥2
	1.7	0.6-5.1	0.323	Adjusted for LVH
	1.5	0.5-4.3	0.483	Adjusted for CAD and dialysis

MPI = myocardial perfusion imaging; OR = odds ratio; CI = confidence interval; CAD = coronary artery disease; Cr = creatinine; LVH = left ventricular hypertrophy.
* Statistically significant adjusted p value between the high-risk and low-risk groups.

the patients were found to have high-risk MPI. The study further showed that almost 72.9% of patients who underwent MPI for the indication of mild troponin elevation had no ischemia detected on MPI. There was no difference in the peak troponin level in patients with and without ischemia. This suggested that mild troponin level itself did not predict the presence or absence of ischemia on MPI. Our hospital used the TnI-Ultra assay, which has been shown to provide significantly improved sensitivity compared to the cTnI assay (6).

Typical chest pain on presentation was associated with a high-risk MPI but atypical chest pain was not found to be an independent predictor. The prior history of CAD, antiplatelet use, diabetes, creatinine >2.0 mg/dL and dialysis were found to be independent clinical predictors of high-risk MPI.

Our study suggests that mild troponin elevation and atypical chest pain were not predictive of ischemia and may not be always helpful in the decision to pursue further evaluation for ischemia. However, in patients presenting with mild troponin elevation, regardless of the clinical symptoms, the presence of significant CAD risk factors such as CAD, diabetes, chronic kidney disease (CKD) and dialysis are more predictive of myocardial ischemia and should be strongly considered in the decision for further risk stratification and evaluation for ischemia and CAD.

It is worth noting that elevated serum creatinine and dialysis are independently associated with detection of ischemia on MPI. Some studies have suggested higher troponin cut offs in renal disease patients for predicting the risk of CAD (7, 8). Coronary angiography is often avoided in patients with renal disease whose troponin values are mildly elevated. Our study suggests that in a patient population with mild troponin elevations, elevated serum creatinine and treatment with dialysis are independently associated with high-risk MPI and further evaluation for CAD with angiography may be warranted, of course after weighing the risks and benefits given the

potential risk for contrast-induced nephropathy in the CKD population (9, 10).

In addition to being retrospective, our study has some limitations. We did not include patients who had mild troponin elevation and went for coronary angiogram without undergoing nuclear stress test, which may be a higher-risk group. Clinical risk factors in our study were obtained from chart documentation and were not independently verified from the patients, while discrepancies have been noted between the medical history documented by healthcare professionals and the reports of the patients with acute coronary syndrome (11).

In conclusion, our study demonstrates that in patients presenting with mild troponin elevation, troponin levels and atypical chest pain did not predict the presence of ischemia on MPI. CAD risk factors such as known CAD, diabetes, CKD and dialysis, were stronger predictors of myocardial ischemia and should be considered in the clinical decision to pursue further ischemic evaluation. Larger clinical studies may be necessary to determine a more accurate diagnostic tool such as a risk score to better predict the risk of myocardial ischemia in patients presenting with mild troponin elevation.

Disclosures

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