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Non-acute myocardial infarction-related causes of elevated high-sensitive troponin T in the emergency room: a cross-sectional analysis

Gregor Lindner · Carmen Andrea Pfortmueller · Christian Tasso Braun · Aristomenis Konstantinos Exadaktylos

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Abstract To systematically investigate putative causes of non-coronary high-sensitive troponin elevations in patients presenting to a tertiary care emergency department. In this cross-sectional analysis, patients who received serial measurements of high-sensitive troponin T between 1 August 2010 and 31 October 2012 at the Department of Emergency Medicine were included. The following putative causes were considered to be associated with non-acute coronary syndrome-related increases in high-sensitive troponin T: acute pulmonary embolism, renal insufficiency, aortic dissection, heart failure, peri-/myocarditis, strenuous exercise, rhabdomyolysis, cardiotoxic chemotherapy, high-frequency ablation therapy, defibrillator shocks, cardiac infiltrative disorders (e.g., amyloidosis), chest trauma, sepsis, shock, exacerbation of chronic obstructive pulmonary disease, and diabetic ketoacidosis. During the study period a total of 1,573 patients received serial measurements of high-sensitive troponin T. Of these, 175 patients were found to have acute coronary syndrome leaving 1,398 patients for inclusion in the study. In 222 (30 %) of patients, no putative cause described in the literature could be attributed to the elevation in high-sensitive troponin T observed. The most commonly encountered mechanism underlying the troponin T elevation was renal insufficiency that was present in 286 patients (57 %), followed by cerebral ischemia in 95 patients (19 %), trauma in 75 patients (15 %) and heart failure in 41 patients (8 %). Non-acute coronary syndrome-associated elevation of high-sensitive troponin T levels is commonly observed in the emergency department. Renal insufficiency and acute cerebral events are the most common conditions associated with high-sensitive troponin T elevation.

Keywords Cardiac biomarkers · Emergency department · Renal insufficiency · Troponin

G. Lindner (✉) · C. A. Pfortmueller · C. T. Braun · A. K. Exadaktylos
Department of Emergency Medicine, Inselspital, University Hospital Bern, Freiburgstrasse, 3010 Bern, Switzerland
e-mail: lindner.gregor@gmail.com

G. Lindner · C. A. Pfortmueller
Department of General Internal Medicine, Inselspital, University Hospital Bern, Bern, Switzerland

Introduction

Troponins are a component of skeletal muscles as well as the myocardium, and current assays are used to detect the cardiac isoforms. Cardiac troponins are used as biomarkers for detection of acute myocardial infarction in the setting of chest pain, electrocardiogram (ECG) abnormalities and cardiac wall abnormalities and their use is recommended by current clinical guidelines [1]. Unlike former tests for cardiac troponins, the new high-sensitivity assays are able to detect circulating troponins in healthy patients without any underlying pathology (high-sensitive troponin T <0.014 mcg/L). However, non-coronary-related conditions were described to cause increases in cardiac troponins which should be considered in the differential diagnosis in patients presenting with troponin elevations [1]. Among the list of putative causes of myocardial injury-related elevations of troponin in patients are acute pulmonary embolism, renal insufficiency, peri-/myocarditis, heart failure or exacerbations of chronic obstructive pulmonary disease [2]. A recent observational study found that age, renal insufficiency and arterial hypertension were risk factors for an elevated troponin T level among patients presenting to the

emergency department with a non-coronary putative cause of troponin T elevation [3]. Another recent large observational study from China confirmed the finding of incidentally elevated serum troponin T levels in patients with renal insufficiency [4]. However, despite the frequent observation of non-coronary troponin T elevations, the causes of elevations of the recently implemented high-sensitive elevation have never been studied systematically in patients presenting to the emergency department.

We aimed to study the prevalence of non-coronary high-sensitive troponin T elevations in patients presenting to a large, tertiary care emergency department and identify the putative causative factors for the elevation. Additionally, we tried to identify factors being associated with high-sensitive troponin T elevation.

Methods

In this cross-sectional analysis, all patients age 16 years or older who received serial measurements of high-sensitive troponin T between 1 August 2010 (implementation of high-sensitive troponin T measurement at our central laboratory) and 31 October 2012 at the Department of Emergency Medicine, Inselspital, University Hospital Bern were included. We included patients with serial high-sensitive troponin measurements (to rule out acute myocardial infarction) only, since a definite myocardial infarction exclusion is better performed on serial measurement of serum troponins. High-sensitive troponin T was determined at the Center for Laboratory Medicine using the Roche Modular E170, an electrochemiluminescence immunoassay. A value of high-sensitive troponin T <0.014 mcg/L, equaling the 99th percentile in a normal collective, is considered normal according to our local reference ranges of the Center for Laboratory Medicine. High-sensitive troponin T levels ordered by the Department of Emergency Medicine were considered for the analysis only. The decision to order a measurement of high-sensitive troponin T was at the discretion of the emergency physician.

Of all patients with measurement of serial high-sensitive troponin T, the following data were obtained by the same two persons (GL, CAP): age, sex, reason for emergency department referral, previously known coronary arteries disease, cardiovascular risk factors (diabetes mellitus, dyslipidemia, arterial hypertension, smoking, obesity, positive family history for cardiovascular events), presence of ECG changes in the emergency department and final diagnosis at the emergency department. Additionally, we obtained data on length of hospitalization and in-hospital mortality. The following laboratory data were gathered: high-sensitive troponin T levels and serum creatinine. We calculated estimated glomerular filtration rate according to the modified diet in renal disease formula (MDRD) [5]. Patients with a diagnosis of acute coronary syndrome were excluded from the study. The diagnosis of acute coronary syndrome was made by the emergency physician in accordance with the cardiologist in charge. The diagnosis of acute coronary syndrome was made at the discretion of the emergency physician by use of patient history, physical examination, ECG and laboratory values (i.e., high-sensitive value). Acute myocardial infarction was diagnosed in line with the current guidelines of the European Society of Cardiology [1, 6]. In case of suspected acute coronary syndrome, cardiologists were informed, who then usually hospitalize patients on their intermediate care ward for monitoring and treatment before potential coronary angiography.

Patients with elevated high-sensitive troponin levels in whom presence of acute coronary syndrome was excluded by serial troponin measurements and serial ECGs were screened for underlying conditions known to be associated with an elevation in cardiac troponins. The following putative causes were considered to be causative for a non-acute coronary syndrome-related increase in high-sensitive troponin T: acute pulmonary embolism, renal insufficiency, aortic dissection, heart failure, peri-/myocarditis, strenuous exercise, rhabdomyolysis, cardiotoxic chemotherapy, high-frequency ablation therapy, defibrillator shocks, cardiac infiltrative disorders (e.g., amyloidosis), chest trauma, sepsis, shock, exacerbation of chronic obstructive pulmonary disease and diabetic ketoacidosis [2, 4, 7–17]. Renal insufficiency was only considered to be associated with high-sensitive troponin T elevation when a CKD-EPI estimated GFR below 60 ml/min was present.

Statistical analysis

All data were collected prospectively and administered in the research database of the Department of Emergency Medicine. All data are presented as means and standard deviation (SD) or medians and first and third quartiles, as appropriate. Mann–Whitney U tests and t tests were performed to compare medians and means as appropriate. Statistical operations were performed by use of Statistica Version 10.0, Statsoft Inc., Tulsa, OK. A p value of <0.05 was considered to be significant for all analyses.

Ethics statement

The study was conducted following the STROBE guidelines and approved by our local institutional review board, the Ethics Commission of the Canton of Bern (www.kek-bern.ch).

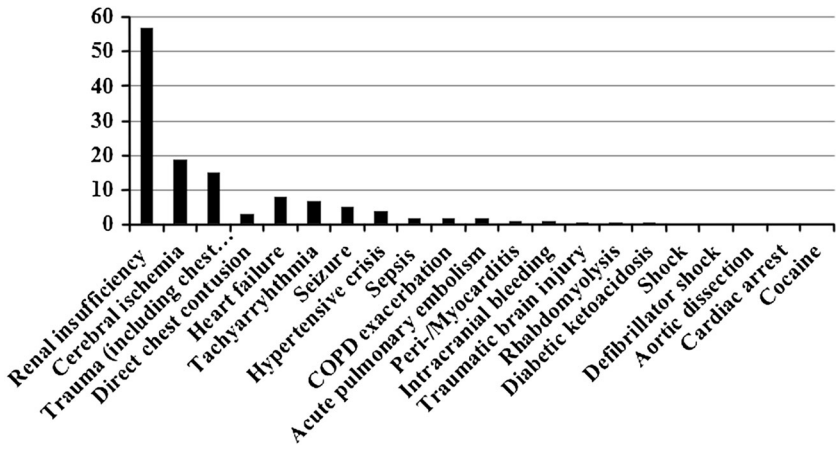

Fig. 1 Overview on the putative causes of high-sensitive troponin T elevation in 506 patients admitted to the emergency department. Numbers given in percent

Results

During the study period a total of 1,573 patients received serial measurements of high-sensitive troponin T. Of these, 175 patients were found to have acute coronary syndrome by clinical, electrocardiographic and laboratory assessment by the emergency physician and the cardiologist in charge leaving 1,398 patients for inclusion in the study. Of these 1,398 patients, 931 (67 %) were male and 467 (33 %) were female. Median age at presentation was 67 years (54–79).

Median level of first high-sensitive troponin T was 0.014 mcg/L (0.004–0.029). 727 patients (52 %) had an initial high-sensitive troponin T level exceeding the normal range of <0.014 mcg/L. Median control values after 3–6 h were 0.015 mcg/L (0.004–0.032). Median change in percent between first and second high-sensitive troponin T determination was 0 % (−5 to 14).

506 patients (70 %) had at least one of the putative causes of troponin T elevation mentioned in "Methods". In 221 (30 %) of the patients, no cause described in the literature could be attributed to the elevation in high-sensitive troponin T observed. The most commonly encountered mechanism underlying the troponin T elevation was renal insufficiency as present in 286 patients (57 %), followed by cerebral ischemia in 95 patients (19 %), trauma in 75 patients (15 %) and heart failure in 41 patients (8 %). A detailed overview of the various potential causes of elevation of high-sensitive troponin T is given in Fig. 1.

High-sensitive troponin T levels according to the cause of troponin elevation are given in Table 1. Patients with a detectable putative cause of troponin elevation had a significantly higher troponin level than patients without a detectable cause (0.029 [0.02–0.054] vs. 0.026 [0.018–0.037], $p < 0.001$). Patients with a detectable putative cause of high-sensitive troponin T elevation were significantly older than patients whose cause for troponin

Table 1 Median and first and third quartile values of baseline high-sensitive troponin T according to the putative cause of troponin elevation

Putative cause of troponin elevation	*N*	Percent	Median baseline troponin	25th percentile	75th percentile
Renal insufficiency	286	57	0.0325	0,021	0.063
Cerebral ischemia	95	19	0.026	0.019	0.06
Intracranial hemorrhage	5	1	0.034	0.02	0.04
Trauma	75	15	0.026	0.019	0.046
Hemorrhagic shock	2	0.4	0.944	0.038	1.85
Seizure	27	5	0.027	0.018	0.032
Heart failure	41	8	0.04	0.024	0.056
Tachyarrhythmia	35	7	0.026	0.018	0.043
COPD Exacerbation	9	2	0.039	0.03	0.05
Hypertensive crisis	22	4	0.0245	0.018	0.063
Acute pulmonary embolism	9	2	0.045	0.022	0.07
Sepsis	10	2	0.047	0.024	0.09
Head trauma	4	1	0.026	0.024	0.028
Rhabdomyolysis	4	1	0.025	0.018	0.035
Peri-/myocarditis	6	1	0.125	0.016	0.373
Diabetic ketoacidosis	3	0.7	0.0725	0.039	0.106
Defibrillator shock	2	0.4	0.0245	0.023	0.026
Aortic dissection	1	0.2	0.024	0.024	0.024
Cardiac arrest	1	0.2	0.097	0.097	0.097
Cocaine abuse	1	0.2	0.074	0.074	0.074

Table 2 Cardiac risk factors in patients with and without non-coronary high-sensitive troponin elevation

Factor	Elevated high-sensitive troponin T ($N = 727$)		Normal high-sensitive troponin T ($N = 671$)		p value
	N	Percent	N	Percent	
Diabetes mellitus	163	22	75	11	<0.0001
Dyslipidemia	220	30	184	27	0.235
Hypertension	281	39	283	42	0.187
Smoking	170	23	214	32	0.0004
Positive family history	40	6	74	11	0.0002
Obesity	73	10	62	9	0.61
ASA	261	36	172	26	0.0001
Clopidogrel	59	8	40	6	0.115
Coumadin	104	14	48	7	<0.0001

elevation remained unknown (74 ± 15 vs. 68 ± 15 years, $p < 0.0001$). Table 2 gives an overview on the cardiac risk factors in patients with and without high-sensitive troponin elevation.

Discussion

In the present study, we found that more than 50 % of patients receiving serial high-sensitive troponin T measurement in the emergency department were found to have non-coronary elevation of the biomarker, i.e., myocardial injury caused by a non-acute coronary syndrome cause. 3–6 h control values remained stable in most patients. Renal insufficiency (eGFR <60 ml/min) was the most common putative cause attributable to the elevation in high-sensitive troponin T as present in 57 % of patients. Cerebral ischemia (19 %), trauma (15 %) and heart failure (8 %) were also commonly observed causes of non-coronary high-sensitive troponin elevation. We found that patients with hemorrhagic shock followed by patients with a diagnosis of peri-/myocarditis had the highest high-sensitive troponin levels.

Recent studies have well described the association between renal insufficiency or age and an elevated high-sensitive troponin T level [3, 4]. However, current guidelines do still lack a clear recommendation on how to handle elevated high-sensitive troponin levels in asymptomatic patients without a concrete suspicion of cardiac ischemia [1]. This is probably due to the lack of data on the absolute values of high-sensitive troponin T levels in these patients, making a statement on what is to be considered normal in the specific patient difficult. Additionally, the mechanisms underlying the troponin elevations in patients of older age or with renal insufficiency have not been clarified so far. The elevation of high-sensitive troponin T in other factors such as acute pulmonary embolism or acute heart failure could potentially be explained by an acutely stressed myocardium by the acute event. In our study, we were able to identify factors associated with an elevated high-sensitive troponin T on admission to the emergency department: presence of diabetes mellitus and use of platelet inhibitors or Coumadin were associated with an elevated high-sensitive troponin T. This is probably due to a higher prevalence of coronary artery disease in these patients predisposing them to myocardial injury in case of an acute event (e.g., sepsis, trauma) according to myocardial stress. However, the lower prevalence of high-sensitive troponin T elevations in smokers remains unclear and might be incidental. It should also be noted that unlike older assays, the new high-sensitivity assays for cardiac troponins are able to detect "normal" concentrations of cardiac troponins that are not associated with an underlying pathology.

Limitations

Our study has some limiting factors which should be of note: the exact history is sometimes difficult to obtain in the emergency department setting. Thus, we cannot exclude that some patients with a history of trauma had unrecognized chest trauma. We can also not exclude that in patients who were unresponsive, all data on the history of coronary artery disease and current medication were obtained completely and accurately. Additionally, it should be said that we were not able to detect a known potential cause of elevated high-sensitive troponin levels in 30 % of patients.

Conclusions

In conclusion, we showed that non-coronary high-sensitive troponin T elevations are common in patients presenting to the emergency department who receive measurements of the biomarker. Renal insufficiency and acute cerebral events were the most common putative causes of an elevated high-sensitive troponin T. Prospective studies should be performed to attempt find a reference range, adjusted for age and renal function, to avoid unnecessary diagnostic procedures in these patients.

Conflict of interest None.

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