Conference Paper

Small Changes in Cardiac Troponin Levels Are Common in Patients with Myocardial Infarction: Diagnostic Implications

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Changes in cardiac troponin (cTn) levels are often evaluated when myocardial infarction (MI) is suspected. The change in the troponin level required for diagnosis is being debated but should exceed the natural biological variation according to current guidelines. Despite this, several reports show that MI patients often present at the emergency ward with relatively stable cTn elevations. In this review we discuss the potential problem using a small cTn change as a way to exclude MI and also provide a possible solution to this diagnostic problem using long-term cTn change.

1. Introduction

When the electrocardiogram (ECG) is inconclusive, the diagnosis of myocardial infarction often involves monitoring of the level of and change in the heart damage biomarkers cardiac troponin T (cTnT) or cardiac troponin I (cTnI) [1–3]. The introduction of high-sensitive cardiac troponin (cTn) assays and the lowering of the diagnostic threshold to the 99th cTn percentile have increased the number of patients presenting with an elevated cTn level that needs further assessment. This is especially prevalent among older emergency room patients, where 36–50% of patients over 65–70 years of age without myocardial infarction (MI) present with an cTnT level above the 99th percentile [4, 5]. In these instances, the change in the cTn level is often evaluated during 3–6 hours and sometimes up to 24 hours [2, 6]. A few hours after cardiac ischemia, the levels of cTn start to increase and reach a plateau phase after 10–15 hour followed by a slow decline [7]. The logic behind evaluating the cTn change is to provide cTn-level-independent evidence of acute myocardial damage. It is often considered that MI can be excluded if the cTn change remains below 20% [1], a criterion based on the analytical imprecision of the cTn assays [1, 2, 8]. On the other

hand, the diagnosis of MI relies on the ability to observe a significant cTn rise and/or falling pattern [2]. The relevant cTn change required for the MI diagnosis is still being debated but must exceed the natural biological variation according to the current European guidelines [6]. There are, however, several reports indicating that many patients with MI present with elevated cTn levels that remain stable during a 1–6 h evaluation period (Table 1). These findings question the use of a small cTn change as a way to exclude the MI diagnosis.

2. Normal Levels of Cardiac Troponin Change

The natural biological variation of cTn levels has been extensively studied in populations without acute myocardial damage (reviewed in [9]). The cTn change can be expressed as the relative cTn change, the percentage of change from a baseline sample, or absolute change, the difference in ng/L from a baseline sample. Relative cTn change is similar at different cTn levels whereas the absolute cTn change increases with the cTn level [4]. Therefore, normal values of relative cTn change can be reported as single value whereas relevant normal values of absolute cTn change must take the individuals baseline cTn level into consideration.

TABLE 1: Studies reporting cTn change in patients with myocardial infarction.

Study cohort	Number of patients in study	Number of patients with MI	Only NSTEMI	Percent of MI patients with <20–25% cTn change during study	Percent of MI patients with <30% cTn change during study	Percent of MI patients with <50–60% cTn change during study	Time during which cTn change was evaluated in the study (h)	cTn change recorded during the hospital stay required for diagnosis	cTn assay used	Symptom time (h) ^b	Reference
Suspected ACS in ER	332	110	No	28%	NR	38%	9.4	No	Roche cobas/Ei70 hs-cTnI	4	[16]
Suspected ACS in ER and patients admitted to the hospital	784	165	Yes	25%	NR	47%	6	>20% or >5 ng/L	Roche cobas/Ei70 hs-cTnI	NR*	[14]
Suspected ACS in ER	454	142	No	5% [#]	NR	11%	24	>20%	Siemens Stratus CS TnI	<8 [§]	[17]
Suspected ACS in ER	381	51	No	25%	25%	NR	6	>20%	Ortho VITROS TnI	3.9	[19]
Suspected ACS in ER	939	200	Yes	51%	0.62	NR	2	No	Roche cobas/Ei70 hs-cTnI	NR	[18]
Suspected ACS in ER	1818	413	No	23%	27%	33%	3	>20%	Abbott Architect STAT high sensitive TnI	4.3	[20]
Suspected ACS in ER	590	65	Yes	36%	NR	50%	2	>4.2 ng/L	Roche cobas/Ei70 hs-cTnI	<12 [§]	[13]

NR: not reported. ACS: acute coronary syndrome. MI: myocardial infarction. CCU: coronary care unit. ER: emergency room. NSTEMI: non ST-elevation myocardial infarction. ^bMedian time since start of symptom at baseline in hours. ^{*}Median symptom time 20 h if <20% change, and median symptom time 12 h if >20% change. [§]Symptom time <8 h or <12 h respectively required for inclusion in study. [#]16% had a <20% cTn change at 6 h.

The normal values of relative cTn change are generally reported as reference change values (RCVs), the range of relative cTn change that includes 95% of all observations in the study population. The RCV for cTnI during a few hours of observation in a healthy population was a rising pattern of 46% or falling pattern of 32% [10]. The RCV for cTnT in a healthy population was 85% [11]. In patients with stable coronary disease [9] or patients admitted due to noncardiac chest pain [12], the RCV for TnI was similar to what was found in healthy subjects (rising pattern of 54–76% and falling pattern of 35–41%). The RCV for cTnT in these studies was actually lower than what was found in healthy subjects (rising pattern of 26–46% and falling pattern of 21–32%) probably due to analytical issues in the previous study [11]. Among patients in a coronary care unit without myocardial infarction, the median relative cTnT change was around 10% and the 97.5th percentile, the upper reference value of relative TnT change, was around 60% [4]. Therefore, relative cTn change above 40–60% is above the natural biological variation and could therefore be regarded as pathological.

The normal value of relative cTn change has not been examined to the same extent [12] as relative changes are different at different cTn levels [4]. However, the absolute cTn change that optimally separates patients with or without MI has been reported. An absolute cTnT change of 7 ng/L during 2 hours of observation [13] and 9 ng/L under six hours of observation [14] was shown to have a superior ability to identify patients with MI compared with the relative cTn change. However, these single cut-off points provided less diagnostic precision among patients with stable cTn elevations [14]. An attempt to find cTn level-stratified cutoff points for absolute cTnT change indicated that 5 ng/L optimally separated patients with MI among suspected acute coronary syndrome patients with a baseline cTnT level below 40 ng/L [14]. Similarly, an diagnostic algorithm derived from the APACE study shows that a one-hour absolute cTnT change of 3 ng/L identified all patients with MI presenting with a baseline cTnT level below 12 ng/L whereas an absolute change of 5 ng/L was needed when the baseline TnT level was between 12 and 52 ng/L [15]. Therefore, when the baseline cTn level is low, absolute cTnT changes above 3–5 ng/L are above the natural biological variation and could therefore be regarded as pathological. When the baseline cTn level is elevated, as often seen in patients with renal failure, heart failure, and old age, the absolute cTn change that optimally separates patients with and without acute myocardial injury is less clear.

3. Cardiac Troponin Change in Patients with MI

The distribution of relative cTn changes in patients with MI have been reported in several studies [13, 14, 16–20] (Table 1). However, since a change in the cTn level is often involved in the MI diagnosis, many of these reports have introduced a circular argument in the study group and thereby reduced their ability to examine the extent of small troponin changes in patients with MI. To establish the true distribution of

cTn change in MI patients, a prospective study is needed where all patients are subjected to angiography, imaging, and functional examinations to obtain cTn-independent evidence of acute myocardial damage of ischemic origin, a study that is yet to be performed. Despite this potential bias in the current studies they often show that over one fifth of patients with MI have short-time cTn changes well within the normal range (Table 1). Although most of the MI patients eventually developed a cTn change above 20% during the hospital stay, as this was often required for the diagnosis (Table 1), the studies indicate that many patients with MI present with stable cTn elevations during the first few hours [14]. The overlap in cTn change among patients with and without MI results in a low diagnostic precision when short-time relative cTn changes are used in the MI diagnosis [13, 16, 20]. These findings questions the requirement to detect a significant rise and/or fall in cTn levels during the hospital stay as an essential part of the diagnosis of MI. Importantly, these data also indicate that it is not safe to exclude MI based on small cTn change recorded during a few hours.

4. The Pathophysiology of MI with Small cTn Change

An important question is why small relative cTn changes seem to be so common in patients with MI? Even if direct evidence is lacking, the available information suggests that small cTn changes are due to presentation late in the infarction process. A small relative cTn change is positively correlated with long symptom time and presentation with high cTn levels at baseline [14] indicating that many MI patients with small cTn changes present close to the plateau phase of the cTn release or later. The possibility that many patients with MI are late presenters fits with the pathophysiology of MI. Close to 50% of the thrombi extracted from coronary arteries in patients with ECG-positive MI show histological signs of being several days old [21, 22], and 75% of all ruptured coronary plaques assigned as the culprit lesion show signs of having ruptured before [23]. In addition, 30–40% of all MIs found in prospective studies are silent, most likely because of diffuse symptoms [24, 25] that, in turn, can be explained by the fact that 70% of ischemic events detected by ECG do not result in chest pain [26].

5. The Use of Long-Term cTn Change in the Diagnosis of MI

Taken together the existing data questions the use of a significant cTn change recorded during the hospital stay as a mandatory part of the MI diagnosis and as a way to rule out MI. It is possible that cTn change evaluated at an outpatient checkup after the event could be an alternative way to diagnose MI. This way of confirming the diagnosis could be applied if the suspicion of MI is low or moderate, the in-hospital cTn levels remain only moderately elevated, and the cTn change is small. In these instances it is possible that the patient could receive a tentative MI diagnosis until a large relative cTn change can be recorded after a week or

two at an outpatient checkup. If these patients, as appropriate after evaluation of the bleeding risk, were started on the same secondary prevention scheme as patients with a firm MI diagnosis, this procedure would add diagnostic precision with little risk to the patient. We are currently evaluating some aspects of this procedure.

Abbreviations

MI: Myocardial infarction
 cTn: Cardiac troponin T
 cTnT: Cardiac troponin T
 cTnI: Cardiac troponin I
 NSTEMI: Non-ST-elevation myocardial infarction.

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