

Chest pain and high-sensitivity troponin: Diagnostic utility

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Abstract

Chest pain is one of the most common causes of emergency department (ED) visits worldwide. Early diagnosis in patients with suspected myocardial infarction (MI) is of paramount importance, in order to timely provide appropriate therapy and reduce the duration of stay in the ED. For this purpose, high sensitivity cardiac troponin (hs-cTn) assays have been developed and are used by thousands of physicians worldwide. Hs-cTn assays are latest generation tests that allow the detection of very low levels of circulating troponin within a short period of time. When used in the context of established algorithms, hs-cTn measurements reduce the time needed for the safe rule-in or rule-out of MI and, consequently, improve the management of patients presenting with suspected acute coronary syndrome (ACS). However, hs-cTn levels can be elevated in several other conditions associated with cardiomyocyte injury; therefore, the clinician should be aware of the caveats of using rapid rule-in/rule-out algorithms. This article presents the diagnostic utility of the hs-cTn assays and summarizes primary principles for their appropriate, safe and effective use in clinical practice.

Key words: *Chest pain; acute coronary syndrome; troponin; rapid rule-in; rapid rule-out*

INTRODUCTION

It is estimated that as many as 20 million patients present to emergency departments (ED) annually in North America and Europe with various symptoms that may be related to myocardial ischemia [1], such as chest discomfort, shortness of breath, nausea, vomiting, weakness and fatigue. None of these symptoms is specific for acute coronary syndrome (ACS) and, thus, diagnosis is often challenging [2]. In the majority of these patients, the final diagnosis is a noncardiac disorder, rather than ACS, such as pulmonary embolism, pleuritis, chest trauma, acute herpes zoster, rheumatoid arthritis, peptic ulcer or gastroesophageal reflux, etc. [3, 4] (Table 1). Until the development of hs-cTn, the application of a work-up in

the ED including clinical assessment (risk factors, symptoms, vital signs), electrocardiogram (ECG) and cardiac biomarkers, resulted in missed MI and inappropriate discharge in ~2% of patients [2]. Missed MI is one of the most frequent malpractices in ED and has great medicolegal consequences. Recently, the use of hs-cTn has decreased this rate and has accelerated the rule-in/rule-out of ACS which is critical for the early initiation of therapy.

Diagnostics

The diagnostic evaluation of a patient presenting in the ED with chest pain (i.e., suspected ACS) should incorporate clinical presentation, physical examination, ECG and hs-cTn measurements in the context of established algorithms.

Clinical Presentation

Acute chest discomfort in ACS patients, usually

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Table 1. Differential diagnosis of acute chest pain [4]

Cardiac	Pulmonary	Vascular	Gastro-intestinal	Orthopaedic	Other
Acute coronary syndrome	Palmonary embolism	Aortic dissection	Esophageal spasm	Musculoskeletal disorders	Anxiety/panic attack
(Myo)pericarditis	Pneumothorax	Aortic aneurysm	Esophagitis	Muscle injury	Herpes zoster
Acute heart failure	Pneumonia		Peptic ulcer	Chest trauma	Anemia
Severe aortic valve stenosis	Pleuritis		Gastritis	Costochondritis	
Takotsubo syndrome			Pancreatitis		
Tachyarrhythmias			Cholecystitis		

presents with retrosternal sensation of pain, squeezing pressure or tightness, that may radiate to the left side of the chest, arm, shoulder, neck, jaw, and/or epigastrium and is precipitated by exertion or stress. Clinical presentation may also include accompanying symptoms such as dyspnea, pallor, nausea, vomiting, diaphoresis, anxiety and syncope. Atypical presentations like isolated epigastric pain, isolated dyspnea or minimal chest pain (i.e., "silent MI") are more common in older patients, women, diabetics and in patients with chronic renal disease or dementia [4,5].

Physical Examination

Physical examination may be helpful for the differential diagnosis of chest pain (Table 1) in patients with suspected ACS. Findings like heart murmurs, irregular pulse, jugular vein distention, blood pressure difference between upper and lower limbs or between arms and friction rub, may suggest an alternative diagnosis. Additionally, the physical examination may contribute to the distinction between non-coronary causes of chest pain (cardiac tamponade, pericarditis, myocarditis, aortic dissection) and extracardiac pathologies (pneumonia, esophageal perforation, biliary colic, acute pancreatitis) [4].

Electrocardiogram (ECG)

The 12-lead ECG at the ED is the first-line diagnostic tool for the evaluation of patients with suspected ACS and should be performed as soon as possible (within 10 min) of the patient's arrival. ECG may be normal in more than 30% of patients with Non-ST-segment elevation ACS (NSTEMI-ACS). However, it may show abnormalities such as ST-segment depression, transient ST-segment elevation or T-wave inversion [4]. Regarding patients

with left bundle branch block (LBBB) and a high clinical suspicion of ongoing myocardial ischemia, they should be managed as patients with STEMI irrespective of the time of LBBB appearance [6]. However, hemodynamically stable patients presenting with acute chest discomfort and LBBB have only a slightly higher probability of having MI in comparison with patients without LBBB. Consequently, hs-cTn measurement has a crucial role in deciding whether to perform immediate coronary angiography or not [7].

Standard and High sensitivity cardiac troponin (hs-cTn)

Diagnosis based solely on clinical assessment and ECG seems to be insufficient for patients with suspected NSTEMI-ACS. Thus, the measurement of a biomarker of cardiomyocyte injury, preferably cTn T or I, is the cornerstone of early diagnosis of MI [4]. Troponins T and I are specific to the heart and are released in the circulation whenever cardiac myocyte damage develops [8].

Recently, the evolution of laboratory techniques has led to the development of new advanced assays, the hs-cTn tests. Hs-cTn tests have a variety of characteristics that differentiate them from the older/conventional troponin test [8]. Firstly, they can detect a much lower serum concentration of cTn with a minimum detection level of 0.005 ng/ml, compared with 0.01 ng/ml when using cTnT (released in 2005) [9]. Moreover, the time frame for the second measurement of hs-cTn can be considerably shortened, due to the rapid detection of any minor myocardial injury [10].

Hs-cTn assays have significant clinical implications compared with standard cTn assays. Most importantly, they have higher negative predictive value for MI and reduce the "troponin-blind" interval leading to earlier

diagnosis of MI. Moreover, they have resulted in a ~20% relative increase in the detection of Type I MI and a corresponding decrease in the diagnosis of unstable angina. High sensitivity tests quantify the amount of cardiomyocyte injury [11, 12]. Therefore, they should be interpreted as quantitative variables and not as a binary system (positive/negative). The higher the cTn blood concentration, the higher the probability of MI; elevations up to 3-fold the upper reference limit have only limited (50-60%) positive predictive value (PPV) for MI and may be associated with various conditions. Higher elevations beyond 5-fold the upper reference limit have high (>90%) PPV for acute type 1 MI [13, 14]. The clinician should be aware of the various conditions beyond MI that are commonly associated with an elevation of cTn. These include cardiac conditions such as heart failure, structural heart disease (e.g. aortic stenosis, left ventricular hypertrophy), tachyarrhythmias, hypertensive emergencies, myocarditis, takotsubo syndrome, cardiac contusion, pulmonary embolism, and non-cardiac conditions such as acute neurological events (stroke, subarachnoid hemorrhage), sepsis, etc. [4,12]. It is noteworthy to mention that patients with cTn elevations have a worse prognosis than those with normal levels of cTn, irrespective of the etiology of troponin rise [15].

False positive measurements may be observed in very rare circumstances, in the absence of cardiomyocyte injury. In these cases, heterophilic antibodies or troponin autoantibodies may be present. Thus, if there is inconsistency between clinical presentation and cTn levels, false positive assay results should be considered [16].

Troponin based strategies for rapid rule-in and rule-out of MI

The novel high sensitivity cTn tests have an important clinical advantage; due to their ability to reduce the time interval to the second cardiac troponin assessment, they allow for a rapid diagnosis of MI in the ED. Thus, rapid strategies for the early rule-in and rule-out of MI have been developed and validated in large multicenter studies [14, 17-19]. Two of these strategies, the 0h/1h algorithm (blood draw at 0h and 1h from patient presentation at the ED) and 0h/2h algorithm (blood draw at 0h and 2h), are recommended (Class I, Level of Evidence B) by the European Society of Cardiology (ESC) (Figure 1) [4].

Diagnostic studies validated these two triage algorithms for patients with acute chest pain and/or

suspected MI, and defined optimal thresholds for rule-out and rule-in. Sensitivity and negative predictive value (NPV) for MI was found to be equal to 99% and specificity and PPV equal to 70%. The 0h/3h algorithm should be considered as an alternative (Class IIa, Level of Evidence B) [20, 21]. These three strategies (0h/1h, 0h/2h, 0h/3h) are based on the absolute change between two measurements of hs-cTn concentration in the blood. The larger the absolute change of cTn levels within 1h, 2h or 3h, the higher the probability of MI [22]. The cut-off concentrations for the 0h/1h and 0h/2h strategies are assay specific (Table 2) [4]. Clinicians should be aware of the specific assay used in the healthcare facility they are providing service, in order to use the proposed algorithms appropriately.

It is important to mention that these novel strategies detect only MI and not unstable angina (UA). The rapid rule-in/rule-out algorithms should always be used in combination with full clinical assessment and ECG, in order to identify patients at high risk, who are unsuitable for early discharge and need further monitoring. Additional imaging tests, such as echocardiography, stress testing, computed tomography angiography (CTCA) or invasive coronary angiography may be important for an accurate diagnosis. Furthermore, these strategies should only be performed after the exclusion of STEMI from the initial ECG, because these patients need immediate perfusion therapy and so the measurement of cTn is not necessary [4, 12].

0h/1h algorithm

If at presentation (0h) the hs-cTn levels are very low and chest pain onset (CPO) is over 3h, MI can be ruled out. Another occasion where MI can be ruled out is the combination of a low initial concentration of hs-cTn at presentation (0h) and the absence of a significant rise within 1h (No 1h Δ). In cases where the hs-cTn levels at presentation are high or when there is significant increase of hsTn value within the first hour (1h Δ), then the patient is ruled-in for MI [4] (Figure 1).

It is important to highlight that the turnaround time for hs-cTn, in other words the time interval from blood draw until measurements become available to the clinician, is about 1 hour. Therefore, the results from the hs-cTn measurements which are performed at 1 hour after ED presentation will be reported back at about 2 hours after the patient's arrival at the ED (1h+1h). Thus, the clinicians can make the decision for rule-in or rule-out about 2 to 3 hours after ED presentation [4].

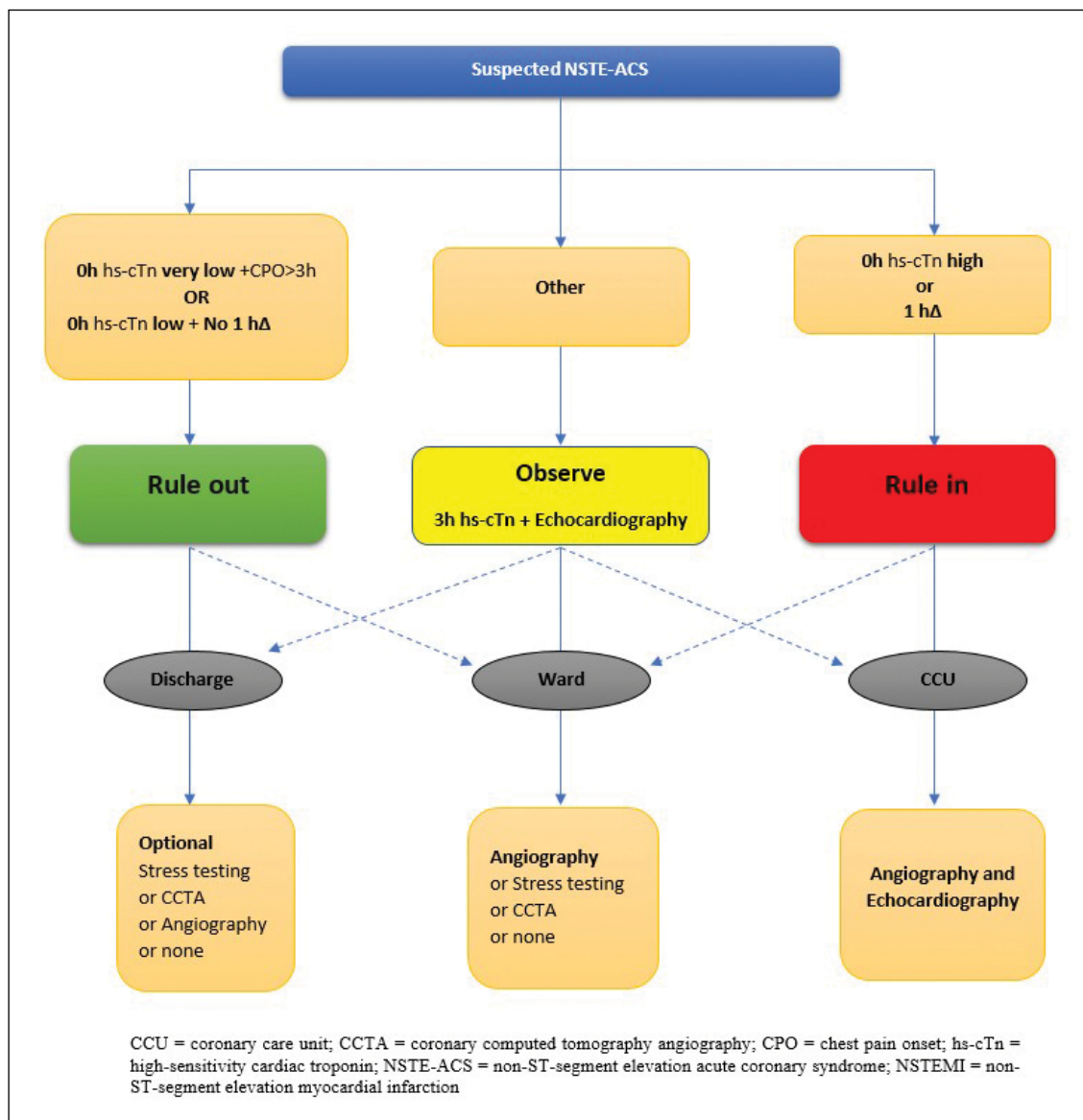


Figure 1. 0 h/1 h rule-out and rule-in algorithm using high-sensitivity cardiac troponin assays in patients presenting with suspected ACS at the emergency department [4].

0h/2h algorithm

The 0h/2h strategy measures concentration changes within 2 hours. Absence of significant 2h Δ , means that MI is ruled-out [4].

0h/3h algorithm

The recent ESC guidelines for NSTEMI-ACS recommend that the 0h/3h algorithm (a rapid rule-out and rule-in protocol with blood sampling at 0 h and 3 h) [23] should be considered as an alternative to the ESC 0h/1h algorithm, if a hs-cTn test with a validated 0 h/3 h algorithm is available [4].

However, evidence suggests that the ESC 0 h/3 h algorithm seems to balance efficacy and safety less well compared with the more rapid protocols (ESC 0h/1h, ESC 0h/2h) [20, 21]

0h/1h vs 0h/3h algorithm

The 0h/1h protocol is preferable in comparison with 0h/3h protocol, due to the fact that the first one allows to rule out more patients than the second one, without an increase in mortality [20]. It is noteworthy to mention that this algorithm has been validated in several multicenter studies and is distinguished for its high

Table 2. Assay specific cut-off levels in ng/l within the 0 h/1 h and 0 h/2 h algorithms.

0 h/1 h algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
hs-cTn I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
0 h/2 h algorithm	Very low	Low	No 2hΔ	High	2hΔ
hs-cTn T (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTn I (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTn I (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTn I (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20

efficacy (PPV) and very high safety (NPV). Furthermore, it is simpler to perform, more rapid and is associated with fewer missed MI situations [4, 20].

Observe zone

Patients who cannot be assigned to the rule-out or rule-in zone, are assigned to the 'observe' zone. These patients constitute up to one third of those evaluated for suspected ACS and are usually men with pre-existing CAD and high long-term mortality [24]. Additional cardiac troponin measurement at 3 hours and echocardiography are the next steps, crucial for accurate diagnosis [24] (Figure 1).

Clinical assessment of mildly elevated cTn levels is integral, because up to one third of patients assigned to the observe zone will finally have a diagnosis of MI or UA. Thus, serial sampling of cardiac troponin at 3h is essential for the differential diagnosis between acute cardiac disease (MI) and chronic cardiac disease. MI is combined with a dynamic cardiac troponin course, while chronic cardiac disease is associated with a more stable hs-cTn elevation [25].

Patients with a high clinical suspicion of NSTEMI-ACS and a relevant change of cardiac troponin within 3 hours should undergo invasive coronary angiography, while patients with a low to intermediate suspicion of NSTEMI-ACS, should be offered noninvasive imaging tests (CCTA) after discharge, or imaging-based stress testing stress echocardiography, positron emission tomography, single-photon emission tomography (SPECT) or cardiovascular magnetic resonance imaging (CMR). In case of special conditions, e.g., rapid ventricular rate response to atrial fibrillation or hypertensive emergency no further diagnostic tests are recommended [4].

Patients with mild hs-cTn elevations

Mildly abnormal hs-cTn levels are just above the 99th percentile (up to 3 times the 99th percentile) and have a broad differential diagnosis [26]. The PPV for patients with acute chest discomfort and mild hs-cTn elevations is very low, about 50% [26]. Therefore, when clinicians are confronted with these challenging patients, they should first consider pre-test probability for MI based on clinical presentation (symptoms and signs) and ECG findings. Moreover, they should think about an obvious non-MI explanation for the mildly abnormal hs-cTn levels, such as acute tachyarrhythmia, acute pulmonary embolism or acute heart failure. They should also consider which diagnostic tests can be useful, such as a repetition of cTn measurement within 1 hour, echocardiography or CMR. Finally, a serious aspect that has to be mentioned, is that hs-cTn elevations, regardless of the cause, are associated with increased mortality. So, further examinations are important [26].

Confounders of cardiac troponin concentration

In patients presenting at the ED with suspected NSTEMI-ACS, besides the presence or absence of MI, there are four clinical variables that affect hs-cTn levels: age, sex, renal dysfunction, time from chest pain onset [4, 8, 12]

According to recent studies, the use of sex specific cut off levels was associated with an insignificant number of patients being reclassified in comparison with the use of a uniform cutoff level [27, 28]. Consequently, the use of sex-specific cutoff levels is not recommended by ESC so far [4]. Further studies are essential in order to determine the advantages or disadvantages of sex-specific cutoff levels in the diagnostic algorithms.

Patients with suspected MI and renal dysfunction are

in a higher risk of MI, than those with a normal kidney function [29]. The diagnosis of MI in these patients is very challenging, because in the first-place patients with renal dysfunction are more prone to an atypical clinical presentation of MI [30]. Moreover, they usually have left ventricular hypertrophy, which can mimic MI findings in ECG. Baseline cardiac troponin concentrations are also chronically elevated in renal dysfunction, in 10-20% of patients for cTn and in up to 70% of patients for hs-cTn, and are associated with poor prognosis [31]. The pathophysiology of high cTn levels is not fully understood, yet.

Even though baseline hs-cTn levels differ between patients with pathological and normal kidney function, there is no difference between them when it comes to measure absolute hs-cTn changes during serial sampling [32].

CONCLUSIONS

Hs-cTn tests combined with clinical evaluation and ECG findings, significantly contribute to the rapid management of patients with suspected MI. Although, these measurements are very useful for the early diagnosis of myocardial infarction, they may also be elevated in several other conditions associated with myocardial injury. Dynamic changes of hs-cTn levels during serial testing are helpful to differentiate ischemic from non-ischemic causes. The most important clinical advantage of hs-cTn assays is the fact that they can be used in the context of novel rapid strategies, allowing for early rule-in and rule-out of MI. Hs-cTn assays not only present a safe, and efficient way for the early detection and management of MI, but they also contribute to a significant reduction of costs and unnecessary investigations in the ED.

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