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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction

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ABSTRACT

High-sensitivity cardiac troponin (hs-cTn) assays have been used clinically by thousands of physicians in many countries throughout the world since their clinical introduction 7 years ago. In the early diagnosis of myocardial infarction (MI), beyond doubt, the most important indication of hs-cTn assays, these simple, inexpensive, and highly reproducible tools complement detailed clinical assessment including chest pain characteristics and the electrocardiogram. Hs-cTn assays for the first time allowed the precise quantification of cardiomyocyte injury around the 99th percentile and thereby substantially increased the accuracy of MI detection from blood obtained at presentation to the emergency department (ED). Higher accuracy at ED presentation enabled the development and extensive validation of early hs-cTn–based diagnostic algorithms, which substantially reduced the time required for the safe rule-out or rule-in of MI. This review summarizes key principles underlying the safe and effective use of hs-cTn in the ED in patients with suspected MI. (J Am Coll Cardiol 2017;70:996–1012) © 2017 by the American College of Cardiology Foundation.

About 20 million patients present with symptoms suggestive of myocardial infarction (MI) to emergency departments (EDs) in North America and Europe each year (1). Patients with MI may present with a wide variety of symptoms, such as chest pain, shortness of breath, weakness, nausea, and vomiting and even fatigue, making the diagnosis difficult (2,3). Demographics, traditional cardiac risk factors, chest pain characteristics, and physical examination can assist disposition decisions, but are insufficient by themselves to identify who does and does not have MI (4-7). Some patients may have objective evidence of a clear-cut diagnosis; however, the majority do not (8). Only a minority will be found to have MI and will instead have symptoms caused by noncardiac and often benign disorders such as musculoskeletal pain, pleuritis, or gastroesophageal reflux, highlighting the medical and economic need of rapid rule-out (9,10). Additionally, the early diagnosis of MI is crucial for the early initiation of evidence-based treatment. Missed MI has important medico-legal implications, being the highest single diagnosis in terms of dollars paid and third highest in terms of

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frequency of claims in malpractice against emergency physicians (11).

HIGH-SENSITIVITY CARDIAC TROPONIN

The clinical assessment, even combined with an electrocardiogram (ECG), is not sufficient to diagnose or exclude non-ST-segment-elevation myocardial infarction (NSTEMI) in most patients, and thus the addition of blood tests to measure the concentration of cardiac troponin (cTn) T or I form the cornerstone for the early diagnosis of MI. Clinicians use cTn values to estimate the likelihood of MI and the short-term risk of death.

Advances in assay technology have led to a refinement in the clinical ability to detect and quantify cardiomyocyte injury (9,10,12–40). These assays increased diagnostic accuracy at presentation, substantially reduced the sensitivity deficit of cTn at presentation for MI and the associated "troponin-blind" interval, and allowed the recent development of several novel strategies for the early rule-out or early rule-in of MI (9,10,12–40). These improved assays are labeled "sensitive" when able to detect cTn in ~20% to 50% of healthy individuals and "high-sensitivity" if they detect a cTn level in >50% of reference (apparently healthy) subjects, and if they have a coefficient of variation of <10% at the 99th percentile upper-reference limit of the assay (10). High-sensitivity assays can accurately detect cTn at lower levels than older-generation assays, giving them higher sensitivity for the detection of MI at presentation, which means that the time interval to the second measurement of high-sensitivity cTn (hs-cTn) can be significantly shortened, thereby reducing the time to diagnosis and improving efficiency in the ED (9,10,12–41).

Although hs-cTn assays have been used in Europe, Australia, New Zealand, Canada, and many other developed countries since 2010, the first hs-cTn assay has just received approval for clinical use in the United States in the spring of 2017. By contrast, sensitive cTn (s-cTn) assays are widely used in the United States.

cTnT and -I are structural proteins unique to the heart. Thereby, cTnT and -I are organ-specific, but not disease-specific markers. High-sensitivity and s-cTnT and -I assays exactly quantify the amount of cardiomyocyte injury (12,27,41,42). They ought to be interpreted as quantitative variables and not in a binary fashion (negative/positive) like a pregnancy test. From a diagnostic perspective, it is highly inappropriate to label a patient as "cTn-positive," as this would lump together patients with only mildly elevated cTn levels barely above the 99th percentile and an associated positive predictive value (PPV) for MI of only about 40% to 50% with patients with markedly elevated cTn levels (e.g., about 5 times above the 99th percentile) and an associated PPV of 90%. The higher the cTn level, the higher is the likelihood for the presence of MI. When referring to levels in the normal range, the same concept applies: the lower the cTn blood concentration, the lower the likelihood for MI. Continuous medical education and training of physicians in these concepts is essential to avoid inappropriate interpretation of chronic mild elevations of cTn associated with, for example, heart failure or other structural cardiac disorders such as valvular heart disease and left ventricular hypertrophy as signs of MI.

TRUE AND FALSE FALSE-POSITIVE hs-cTn MEASUREMENTS

In the absence of overt myocardial ischemia, elevated cTn levels are often labeled as "false-positive" hs-cTn results, which is a misleading term. Most of these unexpected hs-cTn elevations are "true positive" for myocardial injury (rather than MI) and reflect previously undetected or underestimated cardiac disease including valvular heart disease, heart failure, hypertensive heart disease, and chronic coronary artery disease (CAD). Many primarily cardiac disorders as well as noncardiac disorders with cardiac involvement may lead to substantial amounts of cardiomyocyte injury and thereby hs-cTn elevations (**Table 1**) (10,27). It is important to note that cTn elevations universally portend a worse prognosis than otherwise similar patients without a cTn elevation. This is true regardless of whether the patient has heart failure, renal dysfunction, gastrointestinal bleeding, sepsis, respiratory disease, pulmonary embolism, subarachnoid hemorrhage, or stroke, or whether the patient is asymptomatic without known cardiovascular disease (43). Obviously, the medical consequences of cardiomyocyte injury as quantified by cTn elevations will be highly individualized and different from that in patients with MI.

Nevertheless, there are some rare circumstances when high or even very high cTn concentrations are observed in the absence of myocardial injury, for example due to analytical assay interferences with heterophilic antibodies. In cases of striking discordance between cTn measurements and clinical presentation, analytical "false-positive" test results

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADP = advanced diagnostic pathway

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

cTn = cardiac troponin

ECG = electrocardiogram

ED = emergency department

ESC = European Society of Cardiology

FDA = Food and Drug Administration

hs-cTn = high-sensitivity cardiac troponin

LBBB = left bundle branch block

MACE = major adverse cardiac event(s)

MI = myocardial infarction

NPV = negative predictive value

NSTEMI = non-ST-segment elevation myocardial infarction

PPV = positive predictive value

s-cTn = sensitive cardiac troponin

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UA = unstable angina