Identification of myocardial injury in the emergency setting

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Abstract

Within the past decade, the use of biomarkers to detect myocardial injury in the emergency department (ED) has been given increasing prominence as evident by the numerous studies and guidelines documenting their use. This review details the scope of the clinical problem, the history of changes in the definition of myocardial infarction (MI) and the new approaches, as well as suggestions for using laboratory biomarkers in the early detection of MI in the ED.

Keywords

AMI; Emergency department; hs-cTn; Biomarker panels

Introduction

Diseases of the circulatory system continue to be the leading cause for hospitalization and death in Canada [1]. Ischemic heart disease (IHD) is a major disease within this category, with its acute symptoms prompting immediate presentation to the emergency department (ED) and the utilization of resources. Delays to definitive care, including the time required for initial diagnosis, may decrease survival in patients having acute myocardial infarction (MI) [2,3]. Between 300,000 and 500,000 individuals per year in Canada present to ED with chest pain [4]. The burden on healthcare resources that this represents is also high in the United States (US) [5] where the annual number of ED visits in 2005 was 115 million, a 20% increase over the previous decade [6]. Chest pain is the leading ED presenting complaint in the middle-aged population (50–64 years) and second in patients aged 22–49 and 65 years of age or older. In the US, over 13 million “cardiac enzyme” blood tests are

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reportedly performed annually within the ED [6]. The term “enzymes” is a holdover from earlier times since the biomarker cardiac troponin (cTn) has replaced the cardiac MB isoenzyme of creatine kinase (CK-MB) as the gold standard to identify MI [7–10].

Patients with symptoms suggestive of acute coronary syndromes (ACS) often present with various combinations of discomfort (e.g., pain or pressure) in the chest, upper extremity (i.e., neck/jaw), arm, back, or epigastric regions [10]. The pain oftentimes is diffuse and may be accompanied by nausea, vomiting, diaphoresis or shortness of breath [10]. Because symptoms are varied and non-specific especially in the elderly and those with other comorbidities such as diabetes and chronic lung disease, up to 75% of patients evaluated in the ED for ACS are found not to have acute ischemia [11]. This percentage is even higher once one removes high-risk patients such as those with overt disease such as ST elevation MI (STEMI) and those who are hemodynamically unstable. The emergency physician must interpret the cardiac biomarker results in the context of the patient’s history, physical examination, and electrocardiogram (ECG) to reach a diagnosis (e.g., non-cardiac diagnosis, chronic stable angina, possible ACS, and definite ACS). Those patients with definite ACS are further sub-divided into unstable angina, non-ST segment elevation MI (NSTEMI), and STEMI [11]. As its name implies, the diagnosis of STEMI is made via ECG findings. This diagnosis occurs either in the ED or sometimes even in the ambulance on the way to the hospital, and later confirmed with biomarker measurements [7–10]. However, many infarcts do not manifest ST segment elevations. With the rise in sensitivity to cardiac tissue damage afforded by cTn, the ECG-based diagnosis of STEMI now represents less than one third of all ACS patients [12,13]. For these remaining chest pain patients, multiple measurements of cTn over several hours (up to twenty-four [10]) may be required before a final diagnosis can be made [7–10]. Frequency and number of measurements will depend on several factors including, the cTn assay sensitivity.

Earlier diagnosis of patients with symptoms suggestive of cardiac ischemia might improve health outcomes for those identified and treated sooner, and would relieve overcrowded EDs of the significant burden of prolonged monitoring of undifferentiated cases. Thus, there are potential benefits to patients and the health-system arising from the early identification of ED patients with evolving MI. For this reason, some favour point-of-care testing (POCT) with its trade-off of timeliness over the sensitivity, specificity and consistency of core laboratory testing [14]. The main advantage of POCT over laboratory-based testing is the reduction in time associated with specimen transport, and possibly analysis (i.e., shorter turnaround time or TAT). However, implementing any form of POCT, even devices with wide acceptance such as glucose meters, presents resource challenges to ensure consistency [15,16]. Moreover, the analytical sensitivity with POCT of cTn remains a concern, and the newer more sensitive cTn assays being developed are almost always on automated immunoassay platforms [17] and not at the point of care. Therefore, the challenge is to achieve both timeliness and sensitivity through new assays and new approaches to identify evolving myocardial injury in the ED.

Acute myocardial infarction—the recent evolution

Prior to 1999, the WHO criteria for the diagnosis of MI were the presence of any two of the following conditions: (1) symptoms of cardiac ischemia; (2) ECG changes consistent with ischemia; (3) elevated serum “enzyme” concentrations [18]. The biomarkers used to detect cardiac necrosis (cardiac “enzymes”) were not completely cardiac-specific and generally increased with significant non-cardiac muscle necrosis [19–21]. In the 1990s, the emergence of routine, specific, and reliable diagnostic assays for the cardiac-specific troponins, cardiac troponin I (cTnI) and cardiac troponin T (cTnT), led to significant changes in the diagnosis of MI (see Table 1).

With cTn came cardiac specificity—a cardiac marker whose elevations were highly specific for cardiac injury, although there was some cross reactivity with skeletal muscle for the early troponin T assays [22,23]. However, the early problems with the cTn marker were related to analytical sensitivity—elevated concentrations of cTn could be measured, but assumed “normal” concentrations were below the limit of detection (LoD) of the assays.

Nevertheless, because of the improved specificity, in 1999 the United States National Academy of Clinical Biochemistry (NACB) changed its recommendations and elevated cTn became the new standard for the diagnosis of myocardial cell damage, replacing the MB isoenzyme of creatine kinase [24]. The NACB recommendations retained the WHO criterion that an ischemic ECG was evidence of an MI even in the absence of biomarker results. Also unchanged under the NACB guidelines was the prevalence of MI because the upper cTn cutoff values were intentionally chosen to yield a clinical sensitivity similar to that of CK-MB under the WHO definition. More notably however, the NACB guidelines recommended the use of two decision limits (cutoff concentrations) to classify individuals. The NACB authors suggested that a new candidate class of disease, unstable angina with minimal myocardial injury, be defined for patients with measurable cTn concentrations below the high MI decision limit they advocated. “Normal” was defined as a cTn concentration for some assays as below the analytical sensitivity limit or with some below the 97.5th percentile of a normal reference range.

One year later in 2000, the European Society of Cardiology and the American College of Cardiology (ESC/ACC) jointly redefined myocardial necrosis (distinct from infarct) to take full advantage of cTn. Under the ESC/ACC 2000 definition of myocardial necrosis, cTn became the primary tool for diagnosis, and the concept of minimal myocardial damage became obsolete. The single cutoff value proposed for myocardial necrosis was the cTn value at the 99th percentile of a suitable control population. The ESC/ACC task force urged for analytical imprecision at this level of less than 10% [7]. Since this precision has still not been achieved at very low concentrations, many have subsequently suggested the substitute use of a higher cutoff concentration at which imprecision, measured as the coefficient of variation (CV), is 10% [25,26]. However, this higher cutoff was never advocated by the ESC/ACC guidelines [7] and recent data confirm (see below) that the 99th percentile criterion optimizes sensitivity and specificity.

The joint ESC/ACC document clearly stated the new dominance of biomarkers as essential for the diagnosis of acute MI. For example, it was suggested that an abnormal ECG alone in

the presence of a normal cTn should not be interpreted as an evolving MI given the lack of specificity of ECG changes for acute MI [7]. For that reason, regrettably, the ESC/ACC definition did not capture some patients with rapidly evolving MI with classical ECG changes in patients presenting very shortly after symptom onset, and before even the earliest of biomarkers would be expected to reflect cardiomyocyte damage. If these patients survived, the markers would invariably rise but if the patient died before that time, the diagnosis of acute MI would not have been made. This situation was remedied in a Scientific Statement published in late 2003 by the American Heart Association (AHA) that re-instated that a typical evolving ischemic ECG pattern could be considered diagnostic of MI if the patient died soon after the onset of symptoms, even in the absence of cTn increases [8].

The 2003 AHA statement also published criteria that operationalized the use of biomarkers to diagnose MI for epidemiology and clinical research studies [8]. In brief, it was suggested that the diagnosis of MI be made if cTn measurements were diagnostic of necrosis in a setting where ischemia was present clinically. A diagnostic set of cTn markers (diagnostic for necrosis) was defined as containing at least one elevated measurement from an “adequate” set of blood samples taken at least 6 h apart and manifesting a rising or falling pattern [8]. In 2007, the NACB published updated laboratory medicine practice guidelines (Clinical Characteristics and Utilization of Biochemical Markers in Acute Coronary Syndromes) that also recommended blood testing at hospital presentation and 6 to 9 h later [9]. In addition, this guideline added a prognostic utility for cTn, in addition to its diagnostic utility. In patients with a clinical syndrome consistent with ACS, a cTn concentration exceeding the 99th percentile cutoff value is indicative of increased risk of death and recurrent ischemic event [9]. In the fall of 2007, an updated *Universal Definition of Myocardial Infarction* from the ESC/ACC/AHA and World Heart Federation (WHF) also advocated using the 99th percentile and provided additional analytical criteria for classifying an acute and evolving MI [10]. The key point emphasized by the 2007 definition was the need to document a “rise and/or fall” of cTn to characterize evolving myocardial injury. Realizing that some cTn assays in current clinical use lack the analytical sensitivity to identify early changing patterns, both committees suggested a 6- to 9-h time delay from presentation in order to detect patients presenting early after pain onset that could have evolving injury.

For those patients presenting early after pain onset, some suggested the use of other markers such as myoglobin and heart fatty acid binding protein to facilitate an earlier diagnosis of MI [9]. Recent publications (see section below) have shown that many contemporary cTn assays can be used earlier than the recommended timeframe and can provide an earlier diagnosis. Thus, there is a strong opportunity for leveraging the utility of sensitive cTn assays for the early detection of MI and better ED resource allocation. The newer guidelines [9,10] have resulted in the manufacture of even more analytically sensitive cTn assays (e.g., the next generation high-sensitivity (hs)-cTn assays), with additional studies required to systematically evaluate the utility of these new hs-cTn assays.

New approaches and biomarkers for early detection of MI

The cutoff cTn concentration for myocardial necrosis is defined as the 99th percentile in a suitable reference population. Therefore, this value, and hence the utility of the marker, is influenced by selection of the healthy/reference population being assessed, as well as by the precision and the analytical sensitivity of the cTn assays [27–29]. At present, only a modicum of screening is done. There is a need for a better system to develop criteria for these healthy populations so assays can be compared and important issues such as differences related to age, gender, and/or ethnicity can be assessed.

As manufacturers develop more analytically precise and sensitive cTn assays, there will be additional clinical uses for measuring cTn [30]. This has already begun for contemporary assays and will only be accentuated as more sensitive assays are developed. For example, while investigating the importance of an apparent age-dependent increase in cTnI levels, it was demonstrated that low but detectable levels of cTnI, even below the 99th percentile of a normal reference population, are associated with long-term risks for coronary heart disease and death in an older, but presumably healthy, community-based, male population [31]. This finding was not limited to cTnI, as recent data using cTnT also demonstrated that individuals with chronic heart disease may also have persistent elevations of cTnT above the 99th percentile [32]. Furthermore, hs-cTnT elevations in individuals with coronary artery disease (CAD) have also been recently demonstrated, indicating that myocardial injury plays a role in chronic coronary disease as well [33]. Moreover, there are many chronic conditions (e.g., renal failure) in which a poor prognosis is associated with detectable cTn concentrations [9,10,34].

Since detectable levels of cTn with current conventional assays (with concentrations in $\mu\text{g/L}$) are prognostic [31,35–38], there is a need to differentiate between patients presenting to the ED with detectable cTn due to chronic conditions from those with acute conditions, such as plaque rupture. These elevations are importantly prognostic and require follow up evaluation even if patients are not admitted to the hospital. The observed frequency of these elevations will increase as assay sensitivity increases and thus distinguishing acute from chronic elevations will become important. The key appears to be to observe a rise in cTn concentrations, with the changing pattern criteria required for the diagnosis of acute ischemia [9,10,30,39]. Recent, emerging data, have also demonstrated that defining changing cTn concentrations may be useful for risk stratification in the emergency setting [40,41] as well as for serial monitoring in the chronic setting [42–44]. However, the criteria for the delta (i.e., change) will need to be explored and determined for the new hs-cTn assays.

The results from both retrospective [45,46] and prospective [47,48] studies on currently available sensitive cTnI assays demonstrate a reduction in the time required to evaluate patients with ACS by yielding an earlier diagnosis of MI. There are also research-use or pre-commercial hs-cTn assays that are more sensitive, with LoD concentrations in the integer ng/L range, compared to present-day assays in clinical use with LoDs expressed in decimal $\mu\text{g/L}$ [33,47,49–55]. These hs-cTn assays have 99th percentiles near 10 ng/L and achieve the required 10%CV below the 99th percentile [49,51,53]. Initial data indicate these assays may

detect changing patterns of cTn earlier in the course of acute disease [53–55]. In summary, earlier and more frequent measurements with hs-cTn assays may be a worthwhile avenue for detecting MI in the ED setting, capitalizing on their earlier ability to document a changing cTn pattern in acute, evolving injury. Such a strategy also obviates the need for the so-called early rising markers.

Important caveats in this new era of hs-cTn assays

The need for additional studies must be emphasized, as it is extremely important that new laboratory tests, especially ones that are as sensitive as these new hs-cTn assays undergo extensive analytic and clinical validation. Even minor numerical changes arising from pre-analytical or analytical problems could trigger important clinical decisions when one is using assays with such a high degree of sensitivity. For example, in our recent evaluation of the novel Beckman assay, we noted minor differences between serum and plasma samples [53]. Though small, if different specimen types were to be used during a presentation, these minor differences could become important clinically by simulating a changing pattern or by pushing values above the 99th percentile. In addition, clinical validation in appropriate populations (i.e., where the test is clinically indicated) is necessary in the context of concurrent diagnostic tests and treatments. Specifically, we need appropriate observational trials that the new candidate assay can, in fact, predict short-term outcomes better than the current assays. As examples, retrospective studies assessing health outcomes using a research prototype hs-cTnI assay in two different ACS populations [56,57], have indicated that a concentration cutoff of approximately 12 ng/L may identify those at highest risk for death or death/MI one year following the initial event.

One area where there is a critical need for more data is in defining the therapeutic implications of elevations in these novel assays. At present, increases in cTn in the setting of ischemic heart disease leads to a variety of data-driven therapeutic approaches. Such increases are associated with more adverse coronary anatomy and more angiographic evidence of procoagulant activity. Thus, aggressive anticoagulation, anti-platelet agents and an early invasive strategy is indicated and has been shown to improve outcomes. Will this be true for the more sensitive assays? Since patients with stable CAD can also have elevations, it is hard to know as sensitivity increases whether the association with more adverse angiographic characteristics will still hold or whether the therapies which work for more severe degrees of cardiac injury will continue to be effective at lower levels of damage. This advocacy not only applies to new more sensitive tests, but also to new approaches to detect evolving injury by use of a “delta” or “change criteria” to identify the biomarker rise/fall pattern that is required for acute MI. The latter is thought to be essential for distinguishing acute cTn elevations from chronic elevations. It may be that developing a reference change value based on conjoint analytical and biological variation will be valuable, however, analyses will still be required for evaluating data to discern the best clinical values. At present, there is only biological variation data and reference change values (RCV) for one hs-cTnI assay [49], and the change criteria has only recently been applied to health outcomes for current sensitive cTnI assays [40,41] and not the hs-cTn assays. Of interest, an initial analysis exploring change criteria with a research hs-cTnI assay has suggested perhaps an even higher percent change than what has been recommended by the guidelines

and publications [58]. It is also recognized that since calculation of the RCV accounts for both biological and analytical variation that assays that lack adequate precision at very low normal values may have values at the low levels seen in many normals that will be greater than values seen in those with disease who will have higher values closer to the cut off values were assay precision may be better.

Prevention

There may well be additional approaches that could be used in the ED at the time of presentation to identify patients at increased risk for subsequent MI and adverse health outcomes. The processes that gradually compromise circulation leading up to the acute event of an MI have been well described in the literature, and the biomarkers that may herald and precede myocardial injury have been the focus of much research [59–61]. The list of potential biomarkers that may provide prognostic information in the ACS setting is lengthy and includes biomarkers reflecting inflammation, endothelial and myocardial dysfunction, as well as ischemia and injury.

Inflammation is thought to play an important role in the events preceding plaque rupture, with many studies indicating roles of both high sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO) in ACS [62,63]. Interleukin-6 (IL-6), as an earlier mediator of inflammation results in CRP production by the liver [62]. IL-6 has also been reported to be derived from cardiac sources in ACS patients [64,65]. Other biomarkers representing endothelial or myocardial dysfunction may also provide independent prognostic information in the ACS setting [66]. This extends beyond the acute phase, as subsequent measurement of biomarkers representing myocardial dysfunction (e.g., NT-proBNP at six weeks and six months) provides incremental prognostic value [67].

ACS biomarkers used in combination panels of three or more [68–70] may prove to be a superior approach for the early detection of MI and future risk [71]. The diagnostic performance will be determined by the choice of the component biomarkers, as in the past there have been biomarker panels that contained only tests reflecting ongoing myocardial injury (e.g., myoglobin and CK-MB). Although the NACB 2007 guidelines still include the use of the so-called early markers (e.g., myoglobin and CK-MB isoforms) for early detection and/or rule-out of NSTEMI [9], in part these recommendations were based on studies using less sensitive cTn assays that may have enhanced the apparent value of the non-troponin “early” markers [72–75]. When a sensitive cTn assay at the 99th percentile is used in conjunction with these older classical structural biomarkers, it is evident that the non-troponin biomarker panels have limited usefulness in the early assessment of patients presenting with ACS symptoms [48,76–78].

Other potential ACS biomarkers include growth differentiation factor-15 (GDF-15) [79], heart-type fatty acid-binding protein (FABP) [80] and pregnancy associated plasma protein-A (PAPP-A) [81], with the latter biomarker (PAPP-A) illustrating the need for prospective studies controlling for important variables to define its role in the ACS setting [82–86]. These assays may identify those at highest risk, and that information may allow for more aggressive treatment of those individuals. In addition, there is a need to develop markers that

distinguish acute coronary artery disease, and especially events due to plaque rupture, from other causes of cardiac injury. A good clinical marker of procoagulant activity would be very helpful in this regard.

Future testing

Biomarkers that may immediately precede myocardial injury continue to be the focus of much research [59,60]. Previous work [70] has indicated that a combination of biomarkers involved in important pathophysiological events during MI appears to provide both diagnostic and prognostic information that the single markers cannot. Some research has reported on the utility of biomarker panels for risk stratification [68], but not for early detection of myocardial injury, whereas other work has found multi-marker panels to be of limited use [71]. These conflicting observations indicate the need for further studies to refine, validate, and provide the additional evidence of potential efficacy of combinations of markers in a contemporary ACS population. This is especially important for biomarkers that have commercial assays such as MPO, in that there is conflicting data with respect to its clinical utility in the early assessment of patients with chest pain [87].

Equally important are future studies assessing the hs-cTn assays for both early detection and risk stratification [88]. A recent study indicated that, compared to present-day assays ($\mu\text{g/L}$), low levels of hs-cTnI ($>10 \text{ ng/L}$) in an ED chest pain population can identify additional subjects at increased risk for MI/death at 6 months [57]. Future studies may show that an increasing pattern of hs-cTn rather than a cutoff value may be all that is necessary for diagnosis. The single cutoff value will be only necessary when the timing of the events precludes the serial approach.

Newer blood tests used alone or in combination that are assessed in well-designed studies [89] will likely enable a faster diagnosis in the acute setting, thereby reducing the ED length of stay and resource utilization. Ideally, the earlier diagnosis will reduce the morbidity and mortality associated with delayed and missed diagnosis. Gathering this much-needed evidence will require collaboration between the clinical chemistry, emergency medicine and cardiology services during the evaluation, implementation, and routine use of biomarkers for the detection of myocardial injury in the emergency setting.

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Table 1

Summary for MI definitions.

	MI definition	Biomarker stated
WHO 1979 [ref.18]	<p>The presence of any two of the following conditions:</p> <ul style="list-style-type: none"> • symptoms of ischemia • ECG Changes • elevated serum enzymes 	Unequivocal change consists of serial change in serum enzymes, or initial rise and subsequent fall of the serum level. The change must be properly related to the particular enzyme and to the delay time between onset of symptoms and blood sampling
ESC/AC C 2000 [ref 7]	<p>(1) Typical rise and gradual fall (cardiac Troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis with at least one of the following:</p> <ul style="list-style-type: none"> a. ischemic symptoms; b. development of pathologic Q waves on the ECG; c. ECG changes indicative of ischemia (ST segment elevation or depression); or d. coronary artery intervention (e.g., coronary angioplasty) 	Maximal concentration of cardiac Troponin T or I exceeding the 99th percentile (acceptable imprecision at the 99th should be defined as 10% CV) on at least one occasion during the first 24 h after the index clinical event. For CK-MB the concentration must exceed the 99th on two successive samples. Total CK not recommended for measurement Blood for biomarker measurements should be obtained on hospital admission, at 6 to 9 h and again at 12 to 24 h if the earlier samples are negative and the clinical suspicion high.
ESC/ACC/AHA/WHF 2007 [ref 10]	<p>Detection of rise and/or fall of cardiac biomarkers (preferably cardiac Troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:</p> <ul style="list-style-type: none"> • Symptoms of ischaemia; • ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block [LBBB]); • Development of pathological Q waves in the ECG; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 	The 99th percentile remains the cutoff, however the use of assays that do not have independent validation of optimal precision (CV 10%) is not recommended