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EDITORIAL COMMENT

Real-World Application of "Delta" Troponin

Diagnostic and Prognostic Implications*

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Improvement in analytical performance over successive generations of assays for cardiac troponin (cTn) has enabled detection of progressively lower concentrations with acceptable precision. By expert convention (1), assays designated as "high-sensitivity" (hs) detect circulating cTn in ≥50% of apparently healthy persons, with the diagnostic threshold for myocardial infarction (MI) set at the 99th percentile in the population. More sensitive assays have enabled acute MI to be diagnosed and excluded more rapidly. However, low-level elevations of hs-Tn (>99th percentile cut-point) are prevalent in patients with stable structural heart disease, including stable coronary atherosclerosis, ventricular dysfunction, and ventricular hypertrophy, as well as in acute cardiopulmonary conditions without coronary thrombosis. As a result, detection of myocardial injury is increasingly commonplace in clinical practice (2). This evolving epidemiology necessitates discrimination of acute myocardial injury, with ischemia being of principal concern, from chronic elevation due to other heart disease.

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Toward that goal, the Third Universal Definition of MI designated the biomarker criteria for acute MI as cTn >99th percentile cut-point and demonstrating a dynamic (rising or falling) pattern (2). It is believed that dynamic changes in concentration, quantified as the "delta" in cTn over a specified period, will help differentiate between the various causes of myocardial injury. Improved analytical precision of cTn assays has made it possible to identify smaller changes in concentration and supported active investigation of the diagnostic performance of various delta criteria with generally encouraging conclusions (3–7). However, an important "real-world" assessment of the delta by Bjurman et al. (8) in this issue of the *Journal* brings several areas of uncertainty into focus and points to the need for additional research.

It makes inherent sense that acute myocardial injury ought be associated with changes in cTn concentration early after the insult (2). Therefore, the finding of abnormal but stable concentrations over serial samples should differentiate chronic elevation in the setting of structural heart disease from acute injury (2). In contrast, the finding of a dynamic pattern should improve the diagnostic specificity for acute MI. At least 6 studies (Table 1) have suggested an improvement in overall diagnostic accuracy by incorporating a delta criterion at 2 to 6 h; for example, a relative delta increased positive predictive value for MI from 75.1% to 95.8% (5), and using an absolute change criterion improved the diagnostic area under the curve from 0.731 to 0.898 (4). Although criteria of a 20% relative change or an absolute change in the range of 50% of the 99th percentile (e.g., 7 to 9 ng/l with hs-TnT) have both performed reasonably (Table 1), the optimal criteria will vary by individual assay, time between measurements, and the range of troponin elevation (e.g., differing with very small vs larger MIs). These and other uncertainties regarding the delta are reflected in present guidelines, which do not recommend a specific delta threshold (2).

The study by Bjurman et al. (8) reveals another issue relevant to clinical adoption. The investigators evaluated the distribution of delta hs-TnT among 1,178 patients from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry with a final clinical diagnosis of non–ST-segment-elevation myocardial infarction (NSTEMI). Importantly, the diagnostic standard for MI did not include a delta criterion but rather was based on any hs-TnT >99th percentile in conjunction with a clinical history and other diagnostic testing consistent with myocardial ischemia. Incorporating a 6-h delta as either a ≥20% change or ≥9 ng/l, the investigators found that, despite a local diagnosis of NSTEMI, 26% of patients did not meet the 20% change criteria and 12% did not meet the 9 ng/l change criteria. The lack of change was more common (approximately one-third) in patients with low hs-TnT (<100 ng/l). The researchers speculate that the observed lack of change may be due to later presentations, during a plateau phase. Second, in a matched group with a diagnosis of noncoronary chest pain, Bjurman et al. (8) observed a substantially overlapping range of delta cTn, particularly in patients with peak hs-TnT <100 ng/l. As a third critical finding, they found that hs-TnT >99th percentile, whether accompanied by

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Table 1 Studies Suggesting Improvement in Overall Diagnostic Accuracy by Incorporating Delta Criterion at 2 to 6 Hours

Lead Author Year (Ref. #)	Assay	Delta Criteria	Performance	Proportion (%) MIs Missed Using Δ Criterion*	Notes
Apple 2009 (9), n = 381	cTnI (VITROS ES, Ortho-Clinical Diagnostics)	Baseline and 6 h: Relative Δ >30%	Sensitivity 75.0% Specificity 90.6% PPV 55.7% NPV 95.8%	25%	Δ criterion improved specificity from 81% to 91% with decline in sensitivity from 94% to 75%.
Keller 2011 (5), n = 1,818 (1,260 serial)	hsTnI (Abbott Diagnostics)	Baseline and 3 h: Relative Δ ≥250%, and relative Δ ≥20%, (Various other relative Δ criteria were also examined)	Δ Criterion (250%): Sensitivity 32.6% Specificity 99.6% PPV 95.8% NPV 83.7% Δ Criterion (20%): Sensitivity 60.3% Specificity 96.8% PPV 84.6% NPV 89.4%	Δ Criterion (250%): 67% Δ Criterion (20%): 40%	A high relative Δ criterion improved PPV from 75.1% to 95.8% at expense of sensitivity.
Reichlin 2011 (3), n = 836 (590 serial)	hsTnT (Roche) and cTnI (TnI-Iltra, Siemens)	Baseline and 2 h: Absolute Δ hs-cTnT: 7 ng/l cTnI: 20 ng/l	hs-cTnT Sensitivity 89% Specificity 93% PPV 64% NPV 98% TnI-Ultra Sensitivity 93% Specificity 91% PPV 58% NPV 99%	hs-cTnT: 10% TnI-Ultra: 7%	Absolute Δ had higher diagnostic accuracy compared to relative Δ.
Eggers 2011 (7), n = 454	cTnI (Stratus CS, Siemens)	Baseline with ≤24 h: Relative Δ 20%	Sensitivity 95% Specificity 92% PPV 85% NPV 98%	5%	
Mueller 2012 (4), n = 784	hsTnT (Roche)	Baseline and ≤6 h: Absolute Δ 9.2 ng/l Relative Δ 20%	Absolute Δ Sensitivity 89.7% Specificity 74.8% PPV 48.7% NPV 96.5% Relative Δ (20%) Sensitivity 75.2% Specificity 58.1% PPV 32.4% NPV 89.8%	Absolute Δ: 10% Relative Δ: 25%	Optimized absolute Δ appeared superior to optimized relative Δ. Optimized relative criterion was 40% Δ.
Cullen 2013 (6), n = 874	cTnI (AccuTnI, Beckman)	Baseline and 2 h: Absolute Δ 30 ng/l	Sensitivity 77.1% Specificity 95.8% PPV 61.4% NPV 98.0%	23%	Absolute Δ had higher diagnostic accuracy compared to relative Δ.
Bjurman 2013 (8), n = 1,178	hsTnT (Roche)	Baseline and 6 h: Relative Δ 20% Absolute Δ 9 ng/l	NA	Relative Δ: 26% Absolute Δ: 12%	

*Derived from data reported in Bjurman et al. (8).
cTn = cardiac troponin; hs-TnT = high-sensitivity troponin T; NPV = negative predicted value; PPV = positive predicted value.

a delta or not, was associated with higher long-term mortality.

So how do we integrate these findings into the cumulative evidence examining delta cTn? The data from Bjurman et al. (8) indicate that between 10% and 25% of patients with MI could be missed if meeting a delta cTn criterion were required, and they raise caution against strict use of the delta to exclude MI in patients with an otherwise high clinical probability. However, limitations of the study should be recognized. In this retrospective study, diagnosis was based on clinical routine and not formally adjudicated. Also, sampling windows were at the clinician's discretion. Because a rising or falling pattern was not required for diagnosis of MI, it is possible that patients with chronic stable elevations of cTn were misclassified as MI. Nevertheless, as a counterpoint, studies of delta criteria referenced against definitions that incorporate a changing pattern may analogously be critiqued for potentially overstating the diagnostic performance of the delta. This lack of a biomarker-independent "gold standard" is challenging in all diagnostic studies evaluating biomarker strategies. Moreover, the proportion of MIs undetected by the delta in the Bjurman et al. (8) study is similar to data extracted from prior, more positively framed results (Table 1). In addition, even if one

were to assume diagnostic misclassification in the Bjurman et al. (8) study, it is noteworthy that the mortality rate was highest among patients with low hs-TnT values that were stable (<20% delta). Although serial changes may assist clinicians in differentiating between etiologies of injury, the lack of change should not be interpreted as indicative of low risk.

The study by Bjurman et al. (8) also reveals striking overlap between the distribution of delta cTn in coronary and noncoronary cases of myocardial injury and speaks to challenges in using a dynamic biomarker pattern to discriminate MI from other causes of acute myocardial injury such as pulmonary embolism or myocarditis. These other causes may be under-recognized in diagnostic studies that equate an elevated cTn and dynamic changes to a diagnosis of MI, thus overstating clinical specificity of the criteria.

Use of a cTn delta criterion to aid in the diagnosis of MI has a compelling rationale and has improved overall diagnostic accuracy in several studies. However, as reinforced by the provocative data from the Bjurman et al. study (8), further investigation and refinement are necessary before definitive criteria can be reliably recommended. Nevertheless, assessment of serial changes is often valuable when using cTn diagnostically. A significant delta over 2 to 6 h is diagnostic of acute myocardial injury, whatever the cause, and supports the diagnosis of MI in the setting of a clinical story indicative of ischemia. As a rule of thumb, a minimum of a 20% change is a reasonable delta criterion, although larger changes deliver higher positive predictive value and absolute change criteria may perform better at extreme (low or high) concentrations. Defining optimal cut-points requires additional study for each assay. Completed studies reveal an inherent tradeoff favoring greater specificity at the expense of sensitivity with higher delta criteria. When serial cTn values are flat, chronic elevation due to structural heart disease should be considered. However, elevation of cTn with a presentation that is concerning for an acute cardiopulmonary cause appears to be associated with adverse short-term prognosis, whether the cTn is stable or dynamic. Therefore, strategies that include early discharge for patients with abnormal but stable values of cTn require a thorough investigation before considered for routine practice. Ultimately, interpretation of both the magnitude and the pattern of cTn elevation in the overall clinical context is the mainstay of diagnosis.

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REFERENCES

1. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem 2009;55:1303–6.
2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.
3. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124:136–45.
4. Mueller M, Biener M, Vafaie M, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem 2012;58:209–18.
5. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011;306:2684–93.
6. Cullen L, Parsonage WA, Greenslade J, et al. Delta troponin for the early diagnosis of AMI in emergency patients with chest pain. Int J Cardiol 2013 Apr 10 [E-pub ahead of print].
7. Eggers KM, Jaffe AS, Venge P, Lindahl B. Clinical implications of the change of cardiac troponin I levels in patients with acute chest pain—an evaluation with respect to the universal definition of myocardial infarction. Clin Chim Acta 2011;412:91–7.
8. Bjurman C, Larsson M, Johanson P, et al. Small changes in troponin T levels are common in patients with non–ST-segment elevation myocardial infarction and are linked to higher mortality. J Am Coll Cardiol 2013;62:1231–8.
9. Apple FS, Pearce LA, Smith SW, Kaczmarek JM, Murakami MM. Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. Clin Chem 2009;55:930–7.

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