Cardiac troponins (cTns) T and I are exclusively expressed at high concentrations in cardiac muscle and have emerged as the preferred biomarker in the universal definition of myocardial infarction (MI). With the recent introduction of high-sensitivity (hs) assays, diagnostic sensitivity for earlier detection of MI has substantially improved. However, lowering the diagnostic cut-off has increased the detection of myocardial injuries in various non-acute coronary syndrome (ACS) conditions, which are not related to myocardial ischemia, leading to rising difficulties in diagnosing MI in clinical situations. Several approaches, such as serial sampling and incorporation of relative or absolute δ-changes, have been proposed to overcome the limitation of decreased sensitivity for MI diagnosis with hs-cTn assays. Current consensus for rapid rule-in proposes a 20% increase within 3 or 6 h when baseline cTn levels are elevated. In the case of negative baseline values, relative increases ≥50% above the 99th percentile were found to be adequate to improve accuracy of MI diagnosis. Besides improved diagnostic accuracy for myocardial injury, even minor cTn elevations provide important prognostic information, and increased levels of cTn are associated with adverse outcomes in both the ACS and non-ACS condition, irrespective of whether the underlying cause is an acute or chronic illness. Thus, it is highly likely that lowering the diagnostic cut-off with even more sensitive assays might improve risk stratification in both conditions. (Circ J 2013; 77: 1653–1661)

Key Words: Biomarkers; Cardiac troponins; Myocardial infarction; Non-ACS; Risk prediction
histopathology and imaging. Thus, despite the short half-life of cTnT in blood of 90 min, cTnT measurements in patients with MI are characterized by a much wider diagnostic window than are cardiac enzymes.

Until today it has remained unresolved whether cTnT release is a specific indicator of irreversible injury, because the cytosolic pool could eventually leak from cell membrane alterations not associated with irreversibly injury. The brief cTn elevations observed in patients with non-ACS conditions may not be related to irreversible cell necrosis but result from reversible membrane leakage or bleb formation on the cytosolic membrane. Because of the detection of modest elevations of cTn in the blood of presumably healthy subjects, additional modes of release must be considered, such as myocyte apop-

cardial injury.

cTns are compartmented in the myocyte as a major structural (bound) sarcomeric and a small (3–5%) functionally free cytosolic pool. Following membrane injury, both these pools appear in blood, but with different kinetics. In the case of cTnT, the wash out of the unbound pool is markedly affected by residual perfusion of the infarct zone on day 1 post injury and may serve as an indicator of the success of reperfusion therapy and quality of microvascular reflow in acute MI (AMI). Subsequent release of cTnT results from irreversible degradation of the contractile apparatus, which may continue well beyond 2 weeks after the onset of injury. The blood levels measured on days 2–4 of MI thus reflect degradation of the sarcomere and are related to infarct size determined by both

Table. Analytical Characteristics of hs-cTnT Assays

| Company/platform/assay     | Cardiac troponin concentration at: | Amino acid residues of epitopes recognized by C and D MAbs |
|----------------------------|-----------------------------------|-------------------------------------------------------------|
|                            | LoD, ng/L | 99th percentile, ng/L (CV)* | 10% CV concentration, ng/L | C: capture; D: detection; hs-cTnT, high-sensitivity cardiac troponin T; LoD, limit of detection; MAbs, monoclonal antibodies; MTP, microtiter plate. (Adapted from Apple et al with permission.) |
|----------------------------|----------|---------------------------|---------------------------|
| hs-cTnI                    | 1.2      | 16 (5.6%)                 | 3.0                      | C: 24–40; D: 41–49 |
| Abbott Architect**         | 2–3      | 8.6 (10%)                 | 8.6                      | C: 41–49; D: 24–40 |
| Beckman Access**           | 0.2      | 2.8 (9.5%)                | 0.5                      | C: 136–147; D: MAb PA1010 |
| Nanosphere MTP**           | 0.09     | 10.1 (9.0%)               | 0.88                     | C: 41–49; D: 27–41 |
| Singulex Erenna**          | 0.5      | 9 (5.0%)                  | 3                        | C: 30–35; D: 41–56, 171–190 |
| Siemens Vista**           | 5.0      | 14 (8%)                   | 13                       | C: 136–147; D: 125–131 |
| hs-cTnT| | | |
| Roche Elecsys†             | 5.0      | 14 (8%)                   | 13                       | C: 136–147; D: 125–131 |

*Coefficient of variation (CV) at the 99th percentile. **Under development and not available for commercial use. †Available for use worldwide but not cleared by the US Food and Drug Administration for use in the USA.
Redefinition of MI

The higher sensitivity of cTn has resulted in the detection of additional ACS patients with MI who escaped detection by cardiac enzyme assays. Thus, up to one-third of all patients formerly classified by CK-MB as unstable angina are now ruled in by cTn as patients with non-ST-elevation (NSTEMI). In large multicenter trials it has been shown that cTn-positive but CK-MB-negative NSTEMI patients carried the same high risk as patients with CK-MB-positive NSTEMI. Furthermore it has been consistently reported that more aggressive treatment of cTn-positive NSTEMI patients with glycoprotein IIB/IIIA antagonists or early percutaneous coronary intervention (PCI) improved outcome, whereas cTn-negative ACS patients did not benefit from these treatment strategies. These large clinical trials were supported by carefully conducted imaging studies, which indicated a close relationship between thrombus formation on unstable lesions and the rate of cTnT increase, thus proposing an elevated cTn as surrogate for complex coronary artery lesions and micro-emboli. Based on this strong clinical and experimental data base, a task force for the redefinition of MI diagnosis was appointed by the European Society of Cardiology (ESC), the American College of Cardiology, American Heart Association and the World Heart Federation. This group stated in their first version of the universal MI definition, in the year 2000, that cTnT and cTnI are the preferred biomarkers for detection of myocardial necrosis because of their superior clinical sensitivity and myocardial tissue specificity. The latest version of the joint criteria for the universal diagnosis of MI by the task force was released in 2012. Accordingly, MI should be diagnosed if a rise and/or fall of cardiac biomarkers (preferentially troponins) are detected, with at least 1 value above the 99th percentile of the upper reference limit (URL), in the presence of indicators for myocardial ischemia such as symptoms, ECG changes, imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. Furthermore, 5 subtypes of MI were defined according to the mechanism of MI, such as occlusive thrombus, supply-demand imbalance, cardiac interventions etc. Thus, it is wisely stated that the interpretation of an elevated cTn needs careful integration of all available clinical, laboratory and imaging data.

High-Sensitivity (hs) Troponin Assays

In the past decades, conventional cTn assays have undergone significant improvements with respect to analytical performance. In addition, manufacturers have refined their assays, with improved signal-to-noise ratio compared with the prior-generation assays, aiming for improvement of the precision of conventional cTn assays at the lower detection range (Figure 1). Thus, assays with total imprecision at the 99th percentile ≤10% and measurable normal values below the 99th percentile in at least 90% of healthy individuals were classified as ‘high-sensitivity (hs)’ assays. We and others demonstrated the improved analytical performance of the novel hs-cTnT assay compared with the previous generations of the assay. However, the many different cTn assays developed and distributed by diagnostic companies differ markedly in their analytical characteristics and do not all meet the minimum analytical criteria suggested in recent guidelines. Assays from several manufacturers are available for cTnT, but because of intellectual property protection, cTnT assays are still only produced by a single manufacturer (Roche Diagnostics), which is clearly an advantage given the standardization issue associated with cTnT assays. A recent paper published on behalf of the IFCC Task Force on Clinical Applications of Cardiac Biomarkers lists currently marketed cTn assays and newer hs assays (Table).

Diagnosis of MI by hs-cTn

The improved analytical characteristics of more sensitive or hs
cTn assays have substantially increased the diagnostic accuracy in the early period of MI, especially by reducing the time from symptom onset to detection of cTn increase\(^{23,24}\) (Figure 2). In 2 recent, large multicenter trials on consecutive patients presenting with symptoms suggestive of ACS, the diagnostic performance of the more sensitive cTn assays was significantly superior to that of conventional cTn assays.\(^{25,26}\) In the study by Keller et al, patients presenting within 3 h of symptom onset showed an area under the curve (AUC) of 0.96 for baseline cTn values, with an improved AUC of 0.98 for an additional sample obtained 3 h after admission using the Siemens cTn Ultra.\(^{25}\) Similarly, Reichlin et al showed that the more sensitive cTn assays outperformed the standard cTnT assay, enabling earlier diagnosis of MI, particularly in patients with recent onset of chest pain.\(^{26}\) In addition, we recently showed in a large head-to-head comparison of 2 of the more sensitive cTn assays, namely the hs-cTnT assay (Roche Diagnostics) and the Siemens Centaur cTnI Ultra, that the hs-cTnT demonstrated a significantly better performance in receiver-operating characteristics (ROC) analysis as compared with the Centaur cTn Ultra regarding diagnosis of MI using the initial sample\(^{27}\) (Figure 3).

However, lowering the diagnostic cut-off from the 10% CV to the 99th percentile in order to improve sensitivity will also decrease the diagnostic specificity of cTn for MI diagnosis because more cardiac pathologies that are not related to myocardial ischemia will be detected, as demonstrated by Apple et al.\(^{28}\) The fact that non-ischemic or non-cardiac causes of myocardial injury may cause positive cTn results not detectable by earlier generations of cTn assays\(^{29}\) has challenged the use of hs-cTn for MI diagnosis, because of the large proportion of

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**Figure 3.** Direct comparison of 2 of the more sensitive cTn assays (Roche hs-cTnT assay and Siemens Centaur cTn Ultra): the hs-cTnT demonstrated a significantly better performance regarding diagnosis of MI than the cTn Ultra in an ACS cohort (n=1,027). ACS, acute coronary syndrome; cardiac troponin T; hs, high sensitivity; MI, myocardial infarction.

**Rapid early rule-in of AMI with high-sensitivity cardiac troponin**

**Acute chest pain**

| Measurement at admission | Initial hs-cTn value ≤ URL | Initial hs-cTn value > URL |
|-------------------------|---------------------------|---------------------------|
| 3 h later               | hs-cTn value at 3 h > URL + increase >50% of URL | hs-cTn value at 3 h > URL + increase >20% of initial value |
| Optional                | hs-cTn value at 6 h > URL + increase >50% of URL | Evidence of ischaemia* |
| 6 h later               |                           | Myocardial infarction |

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**Figure 4.** Diagnosis of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin (hs-cTn). URL, upper reference limit. (Adapted from Thygesen et al with permission.\(^{39}\))
false-positive cTn elevations.  

To improve the diagnostic specificity of hs-cTn for the diagnosis of MI, which is crucial for decision making about appropriate therapy, analysis of the relative and absolute delta changes of cTn over time has been proposed. However, there are still limited data on the preferred index, such as relative and absolute changes, or the reference change value (RCV), which is calculated from individual short-term or intermediate-term biological variation. Moreover, the magnitude of the kinetic change that best discriminates between acute and chronic increases has not been defined yet. Data in healthy individuals on biological variation assessed by RCV suggest that minor increases in cTn concentration are important when individual short-term or intermediate-term changes, or the reference change value (RCV), which is calculated from individual short-term or intermediate-term biological variation. Moreover, the magnitude of the kinetic change that best discriminates between acute and chronic increases has not been defined yet. Data in healthy individuals on biological variation assessed by RCV suggest that minor increases in cTn concentration are important when using the hs assays.  

Data from Reichlin et al and from our group support the use of absolute δ-changes during serial sampling by showing very high diagnostic accuracy, especially for concentrations close to the 99th percentile. Using hs-cTnT, Reichlin et al found that an absolute δ-criterion of >0.007 μg/L (7 ng/L) within a 2-h period significantly improved the diagnostic specificity for AMI from 93% to 95%. Compared with a relative δ-change, the absolute δ-change provided a superior diagnostic performance for detection of MI (0.95 vs. 0.72, P<0.001). In support, we could demonstrate that kinetic criteria were useful for rule-out of AMI and that absolute changes outperformed relative changes because of their higher specificity in an ACS cohort and in patients with hs-cTnT increases not due to ACS.  

Using absolute changes, a rise or fall of at least 6.2 ng/L in ACS patients and 9.6 ng/L in the entire cohort including non-ACS conditions, was adequate to rule-out AMI. In addition, we found an ROC-optimized relative δ-change of 43.5% in patients with initial baseline cTn levels up to 49 ng/L, which is in the range of what has been recently reported for biological short-term variability. Conversely, others have proposed higher relative δ-changes between 30% and 250%. Previously, Apple et al tested the utility of percentage changes in cTnI of ≥10%, ≥20%, and ≥30%, and reported that ≥30% change in cTn should be used as the optimal change in addition to either the baseline or follow-up concentration to improve specificity for MI diagnosis in patients presenting with symptoms of ACS.  

Our group demonstrated ROC-optimized relative δ-change values for hs-cTnT between 117% and 243% within 3 and 6 h, respectively, for diagnosis of MI in a selected small cohort of patients with evolving MI.  

In conclusion, these data support the use of serial sampling over a short period of time in the diagnostic approach to MI assessment in order to overcome the limitation of decreased sensitivity in the new hs-cTn assays. However, a relative change ≥50% has been found to result in more frequent false-negative results in patients with an index diagnosis of MI. Thus, current consensus for rapid rule-in proposes a 20% increase within 3 or 6 h when baseline cTn levels are elevated. For values below or close to the 99th percentile, increases above the 99th percentile with relative increases ≥50% within 3 or 6 h or absolute increases for hs-cTnT of 7 ng/L within 2 h may be adequate to improve the accuracy of MI diagnosis (Figure 4).  

Concerning the timing of sampling and interpretation of kinetic changes, the recent guideline for the use of hs-cTnT in acute cardiac care suggests that blood samples should be obtained at the time of admission and 3 h after admission. More recently, Reichlin’s group identified a simple algorithm that allowed a reliable rule-out and rule-in within 1 h for the majority of these patients using baseline hs-cTnT values in combination with absolute δ-changes. However, the time interval for sampling should be appropriate to the clinical context of presentation to allow discrimination of acute from chronic reasons for the cTn increase. The interpretation of kinetic changes requires consideration of several variables, including...
the time between symptom onset to cTn sampling on presentation, as well as reperfusion success. Moreover, focusing on kinetic changes within 3–6h after admission, as proposed by the recently published ESC guidelines,39,40 or even within 1h,41 will allow earlier identification of MI but runs the risk of underdiagnosing MI in certain situations, particularly in patients with delayed presentation after symptom onset.35 Accordingly, patients may require additional sampling beyond 3–6h if it is strongly suspected that they have had a MI despite earlier measurements not showing a significant increase in cTn.17,42

**Micro-AMI: Therapeutic Consequences**

The improved diagnostic sensitivity of the hs-cTn assays significantly affects the numbers of MI diagnoses, with an increase in detection of so-called micro infarcts, undetectable by prior-generation assays43 (Figure 5). However, the reclassification of ACS patients by lowering the 99th percentile threshold may translate into better patient care. Previous ACS studies using less sensitive assays have consistently demonstrated that patients with minor cTn increases benefit from an early invasive strategy.13 In addition, even minor elevations of cTn have been associated with coronary artery disease, intracoronary thrombi and adverse outcomes.44–46 Those findings have been confirmed by additional trials using more sensitive assays that also indicated that lowering the diagnostic cut-off concentration improves risk stratification in patients with suspected ACS and that any elevation of cTn conveys important prognostic information47–49 (Figure 6). By comparing the hs-cTnT assay with the conventional 4th-generation cTnT assay at the 99th percentile value, we and others have shown that cTn increases on admission detected by the hs-cTnT assay are independently predictive of an adverse outcome.50,51 In patients with ACS conditions, minor increases in cTn exceeding the 99th percentile threshold demonstrated a 3-fold higher adjusted risk of death and recurrent MI in short-term follow-up at 30 days, but also in long-term follow-up, with a 2.7-fold higher risk at 12 months.52 In a comparison of 2 sensitive cTn assays, the hs-cTnT value at admission was superior to the baseline levels of a sensitive

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**Figure 5.** All-cause mortality by diagnosis at 3-year follow-up according to high-sensitivity cardiac troponin T (hs-cTnT) tertile. ACS, acute coronary syndrome; STE, ST-elevation.

**Figure 6.** Use of hs-cTnT assay and diagnoses in patients from the CPU-Registry of the University Hospital of Heidelberg in consecutive patients presenting with acute symptoms during a 6-month period (n=3,327). Approximately 20% of consecutive patients admitted to the CPU exhibited hs-cTnT increases >99th percentile; however, 69% of hs-cTnT increases were not related to ACS. hs-cTnT, high-sensitivity cardiac troponin T; ACS, acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; UAP, unstable angina pectoris.
cTnI assay for prediction of long-term prognosis.27 Although increases above the URL with less sensitive, conventional cTn assays have helped physicians decisively in guiding diagnostic and therapeutic procedures, the potential benefits from an early invasive strategy among patients with an elevated hs-Tn assay remain elusive. A substudy from the Platelet Inhibition and Patient Outcomes (PLATO) trial evaluating the benefits of ticagrelor, a more potent P2Y12 inhibitor than clopidogrel, found a significant interaction between cTn status and efficacy of ticagrelor vs. clopidogrel. Patients with hs-cTnT values above the 99th percentile and a diagnosis of NSTEMI derived benefits from ticagrelor by reducing cardiac endpoints, regardless of whether they underwent an invasive or a conservative treatment.53 Conversely, patients tested negative for hs-cTnT (unstable angina) did not benefit from ticagrelor as compared with clopidogrel. When treated by PCI, these patients more often experienced procedural non-CABG related major bleeding and had higher rates of the primary endpoint (death or MI), driven by an excess in procedure-related MIs.54 Thus, it appears that patients with unstable angina as defined by hs-cTn assays are a low-risk cohort that may not benefit from treatment strategies outlined for the NSTEMI cohorts. Consequently, the current ESC guidelines recommend not performing early routine coronary angiography in patients who are negative for hs-cTnT, but to base the decision on recurrence of chest pain or a positive stress test.40

The Challenge: Non-ACS Cases
With the implementation of novel hs-cTn assays, not only has the sensitivity for detection of AMI increased, but also the detection of cTn elevations in non-ACS conditions (Figure 7). The high prevalence of patients with cTn elevations in various non-ACS conditions leads to increasing difficulties in diagnosing MI in clinical situations. In patients presenting acutely to an emergency department (ED) with typical symptoms or unequivocal ECG changes, cTn elevations are most likely of coronary origin. However, in the absence of symptoms and findings of myocardial ischemia, other acute or chronic non-ACS conditions must be considered, especially in elderly patients.55 The prevalence of cardiovascular and extracardiac comorbidities increases with age,56 and higher cTn concentrations have been observed in older, presumably healthy, populations.57 Thus, McFalls et al found that only 42.8% of consecutive patients with increased cTn concentration presenting to an ED were diagnosed with ACS and the remaining cTn-positive patients suffered from a wide spectrum of acute and chronic diseases.58 Similarly, Javed et al reported that 65.8% of symptomatic patients admitted to an ED with increased cTn levels did not meet the universal MI definition criteria.58 That observation is in line with several previous studies of different non-ACS populations in which elevated hs-cTn was related not only to acute cardiac pathologies, but also to numerous additional acute and chronic extracardiac conditions.59,60 In the Dallas Heart Study, which used the hs-cTnT assay, increases in cTn were seen more frequently in non-coronary than in coronary artery disease.61

The exact pathomechanism for increased cTn in non-ACS conditions is still elusive. A number of studies have suggested that cTn may be released from cardiac myocytes not progressing to necrosis. The consistent finding of elevated cTn in patients presenting with supraventricular tachycardias and normal coronary angiography support a different mechanism of cTn release.62 However, in many cases of presumed non-ischemic etiology the contribution of myocardial ischemia may not be ruled out entirely and thus some overlap may exist between the supply-demand imbalance seen with type 2 MI and myocardial damage not caused by myocardial ischemia.59

There is an increasing number of studies showing that cTn conveys long-term prognostic information and is associated with an adverse outcome in both ACS and non-ACS conditions, irrespective of whether the underlying cause is acute or chronic.63 Agewall et al demonstrated in unselected patients with suspected myocardial ischemia that mortality rates for patients with non-ACS causes of elevated cTn levels were between 22.8% and 24% for cTn concentrations >0.11 μg/L, and thus were comparable to values for patients with MI ranging between 28% and 24.2%, respectively.64 Non-ACS conditions include acute pulmonary embolism,65 chronic pulmonary arterial hypertension,66 and also stable coronary artery disease.64,65

Recently, we reported on an association between the presence and magnitude of hs-cTnT baseline elevations and rates of death or the composite of death/MI at 3 years, with poorest outcomes among patients with non-ACS conditions.27 In addition, Irfan et al showed that chest pain patients with a non-cardiac reason for hs-cTnT levels >14 ng/L were at increased risk for all-cause mortality (hazard ratio 3.0, P=0.02) during follow-up.66 These findings lead to the conclusion that the number of indications for testing of cTn in settings other than ACS will increase and that measurement of cTn with hs assays should always be considered for risk stratification not only in ACS but also in non-ACS cases.
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