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Laboratory medicine as the science that underpins medicine: the “high-sensitivity” troponin paradigm

Abstract: The availability of so-called high-sensitivity troponin assays (hsTn) has scored a compelling goal for laboratory medicine, allowing the safe clinical application of international recommendations for the definition of acute myocardial infarction (AMI). However, the introduction of hsTn has not been welcomed by clinicians, claiming an increase in false-positive results. Here we critically trace back the steps following the introduction of hsTn by referring to the 5-year practical experience in our academic hospital and to suitable information available in the literature. In agreement with published data, we found that hsTn introduction was associated with an increased number of AMI diagnoses, whereas the test volume, the revascularization rate, and the proportion of cases with negative angiography findings remained virtually unchanged. Fast-track protocols for ruling out AMI have been further optimized to recommend sampling at presentation and after 3 h only. We focus on a cost-effective use of hsTn that can account for all clinical variables increasing the pre-test probability in order to ensure that tests are ordered only for patients at medium to high risk for acute coronary syndrome (ACS). To guide interpretation of results, hsTn typical release patterns suggestive for AMI should be identified by evaluating the significance of concentration changes. hsTn have markedly shortened the time to rule out or rule in AMI and has the potential to improve the prognostic assessment of critical patients in clinical contexts different from ACS.

Keywords: acute myocardial infarction; assay performance; prognosis; sensitivity; troponin.

Introduction

The implementation of so-called high-sensitivity cardiac troponin (cTn) assays (hsTn) has benefited the laboratory through enhanced analytical sensitivity and precision and now its ability to fulfill international recommendations for the “universal” definition of acute myocardial infarction (AMI) that have been released over the past 14 years [1–3]. However, with the implementation of hsTn, emergency department (ED) physicians and cardiologists have been rather confused on the interpretation of marker results [4, 5]. The capability of hsTn to measure cTn concentrations >10-fold lower than those detectable by previous-generation assays, and with highest precision, has unexpectedly complicated patient triage [6, 7]. The trade-off of greater clinical sensitivity for lower clinical specificity for AMI diagnosis has sparked hot debates and discussions involving both clinicians and laboratorians [8–11]. With hsTn introduction, cardiologists claim there is an increase in false-positive results and consider hsTn to be a poorer diagnostic test than previous-generation, less-sensitive assays because hsTn does not fit with the clinical workup [6]. In reply, laboratorians have reminded cardiologists that cTn-positive results only indicate the presence of myocardial injury from various pathophysiological mechanisms and that hsTn enables more accurate detection of “microscopic zones” of myocardial injury [5, 7]. Some clinicians had initially misunderstood the interpretation and the additional diagnostic value contributed by hsTn, underestimating the importance of clinical findings and serial cTn testing [5]. Indeed, the eroded diagnostic specificity claimed by clinicians suggested that
test ordering and result management needed to be better “guided” by laboratorians by utilizing the improved analytical performance of hsTn [6, 11].

It is now clear that the hsTn introduction requires changes to diagnostic rules and algorithms. In this review, we summarize the available evidence showing how broadly the replacement of previous-generation cTn assays with hsTn has changed patient clinical outcome and costs of care. Along with the retrieved evidence, we will trace the steps of hsTn introduction in our academic hospital by reporting the evolution of internal recommendations for ordering and interpreting test results as well as data retrieved by internal audits.

The prequel: before hsTn

If we trace the history of cTn since its clinical introduction, we may realize that it has gained increased relevance from its inclusion in Cardiology Society Consensus Documents for defining AMI. The further adoption of more sensitive assays has required a more detailed definition of the interpretative criteria [1–3]. In the first Consensus Document, released in 2000, cTn was indicated as the preferred test to detect myocardial necrosis, due to absolute tissue specificity and high sensitivity, and an increased value was defined “as a measurement exceeding the 99th percentile of a reference control group” [1]. AMI was tailored on cTn increase secondary to coronary ischemia. The updated 2007 redefinition of AMI confirmed the 99th percentile cutoff “as decision level for the diagnosis of AMI”, cautioning on the need to estimate the 99th percentile reference limit for each specific assay “with appropriate quality control” [2]. It is now known that the selection of “cardio-healthy” reference individuals requires partitioning according to age and gender and that sample size may markedly affect the estimate of the 99th percentile cutoff [12]. By fixing the decision limit to the 99th percentile value, one theoretically maximizes the capability of cTn to identify subjects with causes of cTn release other than physiological cardiomyocyte turnover, not to diagnose patients with AMI. More importantly, the detection limit (LoD) and the analytical performance of the assay may strongly influence the definition of the 99th percentile cutoff since this implies that cTn concentrations in the majority of subjects (if not all) should be detectable [12]. Apple and Murakami showed, however, that commercial assays were unable to detect cTn in up to 98% of apparently healthy subjects [13]. Therefore, under these conditions, a frequency distribution of cTn values in a reference population cannot be defined, and the derivation of the 99th percentile is flawed. In addition, the lack of analytical sensitivity is associated with a high measurement error at the very low cTn concentrations corresponding to the 99th percentile cutoff and implies that there is a high risk of misclassifying positive and negative results for myocardial injury [14].

The manufacturers’ reaction: introduction of hsTn

To adjust the misfit between guidelines and the analytical performance of available cTn assays, manufacturers aimed to improve the analytical sensitivity and imprecision of their assays [16]. Accordingly, several approaches were proposed to achieve the accurate measurement of cTn concentrations, even down to the nanogram per liter expected to characterize healthy people [18]. For instance, in the Roche Diagnostics hsTn determining cardiac troponin T (hsTnT), the improvement in the analytical signal has been achieved by increasing the sample volume and decreasing background noise through optimization of buffer composition. A first prototype assay was already available in 2003, when a first multicenter pilot study was performed. However, this first version of the hsTnT assay was never marketed, even if a clinical study using it was later published [19]. Four years later, a development version of hsTnT was proposed and externally evaluated [20]. Finally, in 2008, a final hsTnT version was evaluated in a multicenter trial and released on the market 1 year later, replacing the conventional assay [21]. In our hospital, we introduced in clinical practice the hsTnT on July 2009 and performed the first internal audit 3 months later (see below). The described steps are summarized in Figure 1. The published trial derived the 99th percentile reference limit in a consistent population of healthy blood donors by setting it at a cTn T concentration of 14.2 ng/L.
In particular, it was observed that 32% of individuals had cTn concentrations above the assay LoD, i.e., >5.0 ng/L, as defined according to the Clinical and Laboratory Standards Institute EP17 standard [22]. At the 99th percentile concentration, comparable results across multiple platforms and laboratories were obtained, and the estimated inter-laboratory CV result was approximately 6.5% [21]. Afterward, our internal quality control data on pooled human serum with a cTn T concentration close to the 99th percentile cutoff confirmed these results, reporting an average imprecision far below the proposed minimum goal for CV of 10% [15]. External quality assessment surveys on samples with average cTn T concentrations around the 99th percentile limit confirmed that ≥99% of participating laboratories using hsTnT met the desired quality level, with a measurement total error <22.5% [23, 24].

The (quiet?) chaos: increasing cTn positivity rates

The increase in positive cTn results may be considered typical of new assay generations increasing the analytical sensitivity of measurement, even when hsTn were still unavailable. For instance, Melanson et al. [25] reported that the changing generation of Siemens cTn I assay resulted in an increase in positive test results by 44.2% hospital-wide and by 114.4% in the ED, without a significant change in test volume. More recently, others have found that 20% of consecutive patients admitted to the chest pain unit had an hsTnT elevation, and in 69% of cases, this was not due to acute coronary syndrome (ACS) [26]. Our audit reported data on the hospital-wide impact of replacing the fourth-generation cTn T assay with hsTnT showed that the absolute number of positive cTn results increased by 95%, corresponding to a relative increase by 111% of positive patients, with no significant change in test volume [27, 28]. By selecting only ED requests, the increase in positive cTn results amounted to 144%, corresponding to a relative increase of 133% in positive patients, with the rate of test ordering still significantly unchanged [27, 28].

From its initial advent, cTn, although providing higher sensitivity for small injury and virtually absolute specificity for myocardial damage when compared with creatine kinase MB (CK-MB) isoenzyme, left some aspects open to discussion [29]. At that time, some authors already underlined that the cardiac specificity and sensitivity of cTn measurement could be a two-edged sword when this marker is used in clinical practice [30]. If we focus our attention on the comparison of rates of positive cTn results between assay generations, it is apparent that lowering the cutoff at the 99th percentile limit and increasing the assay sensitivity has resulted in (a) a shift from diagnoses of unstable angina (UA) to AMI and (b) more cases of cTn increase caused by non-ischemic cardiac necrosis. The World Health Organization, during 2008–2009, reported there was a relevant shift from diagnoses of UA to AMI [31]. This demonstrated that the definition of UA is strongly influenced by the assay used to measure cTn and will be affected by the implementation of hsTnT, namely by the increased capability to detect very minor myocardial necrosis [32].

Fixing the cTn cutoff at the 99th percentile: a trade-off between sensitivity and specificity?

Initially, cardiologists recommend using the 99th percentile cutoff when assays were unable to measure cTn accurately. However, currently, when the new generation of hsTn can finally fulfill the AMI recommendations reliably, cardiologists generally have not welcomed their introduction. In this regard, several authors have remarked the need to differentiate between the specificity of cTn for cardiomyocyte injury and its clinical specificity for AMI [33]. In particular, the improved sensitivity of cTn assays has reinforced the evidence that the 99th percentile limit, if applied to only one result, is not functional to the diagnosis of AMI. Only serial testing allows for the discrimination of acute from chronic pathophysiological mechanisms of cTn release. Pathophysiological release of
cTn is characterized by an increasing (or decreasing) cTn pattern, indicating an acute disease process, whereas an unchanged stable cTn course indicates a chronic clinical condition (Figure 2) [34]. Indeed, the 2007 universal definition of AMI stated that “the detection of an increase and/or decrease in cTn with at least one value above the 99th percentile limit” is the biochemical criterion to diagnose AMI, together with the clinical or instrumental evidence of coronary ischemia [2].

Importantly, if we dichotomize typical/atypical cTn curves (built on two to three serial measurements), in addition to at least one cTn value above the 99th percentile limit, an additional decisional criterion, related to the entity of increasing/decreasing of cTn trend, should be defined to characterize cTn patterns typical for acute myocardial necrosis. Currently, there is no general agreement on the definition of changes (δ) suggestive for acute conditions [35]. In our daily clinical practice, we defined as “typical” an increasing or decreasing pattern showing a cTn T change between two consecutive samples exceeding 50% for increasing cTn T results and 30% for decreasing results [27, 28]. Otherwise, the cTn pattern was considered “atypical”. For the definition of these δ percentages (estimated as reference change value), we refer to the short-term biological variation for cTn I [36] because, unfortunately, published studies that tried to assess biological variability of cTn T were implausible, as the majority [37] or a significant number [38] of cTn T results in selected individuals were lower than the LoD. One should be aware, however, that cTn I and cTn T may have different biological kinetics in blood, so their biological variation might be different.

To compare the clinical impact of hsTnT, we retrieved cTn curves (at least two results during patient examination) of comparable 3-month periods before and after hsTnT implementation and selected conventional cTn T assay and hsTnT curves with typical marker release (δ>50%) [28]. Although an increase in positive individual cTn results and in positive curves was detected using hsTnT, the proportion of positive curves with δ>50% did not change (Figure 3). This was an important proof confirming that, if the scrutiny of cTn release kinetics in blood is performed, the use of hsTnT does not imply lower specificity for diagnosing AMI. Meanwhile, any effort to optimize the evaluation of a single cTn value by a decisional level is diminished by the biological behavior of the marker. According to the estimation of cTn biological variation, the far lower within-person variation with respect to the inter-individual variation implies a very low index of individuality (i.e., ratio of within- to between-subject variances) [36]. Under this condition, an isolated dichotomized interpretation of cTn results, resorting to the 99th percentile limit, can be misleading, and this agrees with clinical evidence and cardiologists’ perception. As described above, the longitudinal monitoring of serial cTn changes is undoubtedly more effective in classifying patients with acute or chronic structural heart disease. Accordingly, a number of algorithms incorporating both baseline hsTn concentrations and changes in values over serial measurements have been proposed to address marker specificity concerns and to allow more accurate ruling out and ruling in of AMI [39].

Figure 2 Temporal patterns describing different types of cardiac troponin variation between consecutive samples in one patient.
The major problem in the practical application of the δ approach is that most cTn tests are ordered just once without any follow-up on biomarker concentrations. In our hospital, approximately 60% of hsTnT results refer to the one test ordered at ED presentation only [28]. This clinician behavior has been confirmed by other audits in similar settings [40] and strongly suggests that laboratories should provide tools to clinicians, e.g., hsTn results with an automatic calculation of δ provided a second sample is collected within a time frame of no more than 12 h [41].

Regarding the triage of ED patients, our experience showed that the hsTnT implementation did not significantly change the rate of admissions in intensive and non-intensive care facilities despite the 2.5-fold increase in positive cTn tests and the 2-fold increase in patient hospitalization [42]. Importantly, although the rate of discharged patients with at least one hsTn-positive result increased significantly compared with the conventional cTn T assay (26.6% vs. 8.5%), the number of patient readmissions after 2 months of follow-up did not significantly increase [42]. The lack of short-term implications suggests that patients with mildly increased hsTnT concentrations and no signs of ACS do not necessarily need hospitalization, confirming that triage decisions in the ED should not only be based on hsTn results but should be interpreted together with other available clinical information [43].

The clinical context to avoid “troponin consult”

As for all the tests used in laboratory medicine, the capability of hsTn results to correctly identify or exclude an AMI [i.e., their positive (PPV) and negative (NPV) predictive values] strongly depends on the prevalence (pre-test probability) of the disease in the clinical setting in which the test is applied. To this regard, the ACS prevalence in ED amounts to a maximum of 10%–12% of admitted subjects with suspected chest pain symptoms, and it is different from the 40%–50% prevalence expected by cardiologists in their selected setting. This is relevant, for example, for a test with 90% sensitivity and specificity at a fixed cutoff point where the PPV may change from 85.7% to 50% and the NPV from 93.1% to 98.8% just by shifting the disease prevalence from 40% to 10%. Thus, by applying hsTn in a setting with low prevalence of acute ischemic damage, a positive marker result is less likely associated with the presence of AMI. The concept was originally raised in 2002 in a commentary published by a joint cardiologist-laboratory group stating that “with the purpose of limiting the number of cases with a finding of myocardial damage in the absence of an AMI, it is advisable that cTn measurement be limited to those patients with a medium to high probability of acute myocardial ischemia...indiscriminate cTn measurement in patients who are evaluated in an emergency or critical clinical setting is to be avoided” [44]. Particularly, with the introduction of hsTn, ED physicians should develop and use well-validated protocols exploiting the whole clinical information in order to increase the pre-test probability, and consequently, the test PPV, before requesting cTn. Clinical judgment becomes more important with new than with conventional cTn assays; type of symptoms, age and gender, presence of cardiovascular risk factors, history of cardiovascular disease (CVD), impaired renal function, atypical electrocardiographic changes, and so on may all significantly predispose to a higher risk for ACS and indicate (or not) the need for hsTn ordering. Very recently, an authoritative group has highlighted in a clear recommendation when hsTn should be requested (Table 1) [45].

Are there better alternatives to the 99th percentile cutoff?

Thresholds alternatives to the 99th percentile limit have been proposed to limit the number of “false-positive” hsTn results. A classical approach to derive decision limits is to use receiver operator characteristic (ROC) curves to identify the cutoff representing the best compromise between test sensitivity and specificity. Using ROC curves, Reiter et al. [46], evaluating the diagnostic performance of hsTnT in >70-year-old patients presenting to the ED with acute chest pain, derived a best cutoff of 54 ng/L, which is far higher than the manufacturer-defined 99th percentile cutoff of 14 ng/L. As expected, the increase in the

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<th>Table 1</th>
<th>The clinical context in which the request of hsTn is justified. Adapted from ref. [45].</th>
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<td>– The measurement of hsTn is indicated in patients presenting to the ED with ongoing or previous chest pain.</td>
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<td>– The measurement of hsTn should be considered in patients without chest pain, but who have one of the following symptoms leading to the suspicion of ACS: sudden onset isolated dyspnea, diaphoresis, palpitations, nausea/vomiting, sudden fatigue, an acute confused state, or syncope.</td>
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<td>– In case of symptoms listed under item 2, the hsTn measurement should be requested in patients with at least one of the following conditions: previous stroke, previous heart failure, diabetes mellitus, age &gt;75 years, female gender.</td>
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threshold concentration markedly increased the specificity of the test (from 49% to 96%), shifting the PPV from 38% to 86%, decreasing the NPV (from 99% to 93%), and resulting in a relevant decrease in AMI cases [46].

As emergency medicine is constantly seeking safe ruling-out processes, the minimum standard for the accuracy of a ruling-out discharge pathway for chest pain should be at least 99% NPV [47]. Body et al. [48] have achieved this NPV using the limit of blank (LoB) of hsTnT (3 ng/L) as decisional threshold at patient admission. However, the impact of this strategy has been criticized, as an undetectable hsTn at admission does not necessarily mean patient discharge and a very early rule-out concerns only a minority of subjects presenting to the ED (only 5 individuals out of 150 per day) [49].

Other studies have pointed out the relevance of achieving both rapid rule-out and rule-in of AMI. Reichlin et al. [50] have proposed a diagnostic algorithm including two serial hsTnT measurements at ED presentation and after 1 h, respectively. AMI was ruled out with an NPV of 100% if the former result was <12 ng/L and the absolute δ at 1 h was <3 ng/L. Patients with baseline values ≥52 ng/L or absolute δ≥5 ng/L were ruled in for AMI with 84% PPV. The intermediate group of patients (corresponding to 23% of tested subjects) remained under observation, further resulting in a prevalence of AMI of 8%. The lowest 30-day mortality for early discharged patients substantially supported the effectiveness of this approach. This study was designed accounting for the data by Mueller et al. [51] reporting that an absolute hsTnT δ change of 6.9 ng/L appears to be superior to the relative δ change for excluding an AMI. Currently, a multicenter clinical trial is aiming to prospectively validate the diagnostic performance of this algorithm in the early AMI diagnosis.

### The sequel (toward absolution):

**optimizing diagnostic sensitivity and specificity**

We have previously reported that when replacing conventional cTn T assay with hsTnT, the proportion of curves displaying a typical pattern of marker release did not change (Figure 3). An audit of typical positively raising hsTnT patterns with at least three cTn results showed that 87.5% of these were elevated already by the first sample, and the remaining became positive for the second sample, 6 h after collection of the first blood at admission. Conversely, by assaying cTn T using conventional assay, only 60.4% of typical raising curves were positive on the first sample, 32.1% became positive on the second at 6 h, and 7.5% on the third one collected 12 h after admission. The difference in sensitivity between cTn T and hsTnT at different sampling points was statistically significant (p<0.001) [28]. The early increase typical of hsTn was further confirmed in a specific study comparing hsTnT with the conventional cTn T assay in 150 patients admitted to ED with suspected ACS (ST-elevation AMI excluded) [52]. A 100% sensitivity for non-ST-elevation AMI (NSTEMI) diagnosis was already achieved by hsTnT within 3 h from admission, whereas the conventional cTn T assay did not reach this performance even after 6 h. By considering the admission result, diagnostic sensitivities of 87.1% and 58.1% for hsTnT and for the standard assay, respectively, were estimated [52]. Using hsTn, a typical increase was always detectable within 3 h from admission vs. 6–12 h for previous less sensitive generations of cTn assays (Figure 4).

With this diagnostic anticipation becoming evident, a change in guidelines was addressed to recommend fast-track rule-out hsTn protocols, i.e., samples drawn at patient presentation and after 3 h as well as the identification of typical cTn changes within curves with at least one value above the cutoff [53]. This optimized diagnostic approach resulted in an advantageous cost-benefit ratio. By comparing the 3-h diagnostic protocol for hsTnT with the conventional 10-h protocol using the fourth-generation cTn T assay, the incremental cost-effectiveness ratio (or cost per total quality-adjusted life years gained) was approximately 4-fold lower for hsTnT 3-h testing [54]. This result is further reinforced by the consistent reduction in morbidity and mortality due to the enhanced capability of hsTn to identify patients at high risk for short-term cardiovascular events (AMI and/or death at 3–12 months) [55].

Figure 5 summarizes the diagnostic algorithms currently employed in our hospital, which integrate all the evidence-based information reported above. Importantly,
for the group of patients with baseline hsTnT concentrations >15 ng/L and δ<50% at 3 h, we suggest to consider an adverse prognosis and possibly retest hsTnT at 6 h. A question that remains is: what is the optimal treatment of the NSTEMI cases, previously reported as UA, that were only detected by hsTn? As recently suggested, this reclassification creates a need for novel prognostication models that would identify patients at different levels of risk and thus guide treatment decisions (i.e., conservative vs. invasive approach) [56]. Notably, hsTnT implementation in our hospital was surely associated with an increased number of NSTEMI diagnoses (from 8% to 11% of ED patients admitted with suspected ACS), but without a significant increase in cases with negative angiography findings, even if NSTEMI patients detected with hsTnT had less extended coronary artery disease (CAD) with respect to those diagnosed by conventional cTn T assay (unpublished data). Interestingly, the revascularization rate and the proportion of percutaneous transluminal coronary angioplasty stent and coronary artery bypass graft (CABG) procedures have remained unchanged.

This is not the end: other pieces to the puzzle

When hsTn is used in clinical frameworks other than type 1 and type 2 AMI, specific thresholds or categories need to be established. Peri-procedural AMI is still an area of intense controversy concerning the use and interpretation of myocardial necrosis biomarkers. The 2011 guideline by American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (SCAI) indicates that CK-MB and/or cTn should be measured in patients symptomatic for AMI during or after percutaneous coronary interventions (PCI) as well as in asymptomatic patients with persistent angiographic complication [57]. However, no interpretative indications or cutoffs are given. The universal definition of AMI, released 4 years before, indicated that, in these patients, a 3-fold increase above the 99th percentile limit of CK-MB/cTn (assuming a normal value at baseline) should, by convention, be defined as AMI (type 4a) [2]. Unfortunately, this was fully arbitrary and not supported by any scientific evidence or soundly anchored to outcome data [58]. Furthermore, the different analytical and clinical performances of biomarker assays were not considered, as it is clear that a CK-MB or a cTn 3-fold increase above the respective 99th percentile limits may reflect infarct sizes of a different degree that cannot be compared due to the huge difference in biomarker sensitivity for detecting myocardial damage [59]. Given these pitfalls, the 2007 universal definition of peri-procedural AMI was not embraced by the interventional community [60]. Recent data from the US National Cardiovascular Data Registry have reported that most institutions do not routinely check cTn post-procedure, being reluctant to include in their diagnostic
armamentarium a test of unclear prognostic meaning [61]. Although limited, outcome data on cTn after PCI are, however, available. A study performed at the Karolinska Institute in Sweden reported that only cTn T concentrations >300 ng/L (i.e., 15 times the 99th percentile limit) measured at 06:00 am after PCI were associated with a significant increase in the risk of death or non-fatal AMI (hazard ratio 2.81, 95th confidence interval 1.32–6.00) [62].

In the third universal definition of AMI, the recommendations for diagnosing type 4a AMI (i.e., AMI related to PCI) have been revised, and once again in an arbitrary way, a peri-procedural AMI defined by a cTn elevation greater than the local 99th percentile limit in patients with normal baseline values, when associated with either clinical symptoms or signs suggestive of myocardial ischemia [3]. This was, however, again ignored in the expert consensus document by SCAI updating the definition of clinically relevant AMI after coronary revascularization [63]. CK-MB remains the recommended marker, and cTn use is suggested only in the absence of CM-MB measurements, with a cutoff (to be used within 48 h of the PCI) ≥70× the local 99th percentile limit or ≥35× when new pathological Q waves appear at electrocardiogram. These recommendations are valid after both PCI and CABG procedures; furthermore, the use of hsTn to assess post-PCI or CABG myocardial necrosis is specifically discouraged [63]. This position is, however, prone to criticism because both the absolute concentrations and the relative increase in cardiac biomarkers are far higher after CABG with respect to PCI [64]. Moreover, hsTn, specifically designed to detect lowest concentrations with high precision, displays higher cTn concentrations, such as those detected after CABG, results comparable to those of previous generations being therefore usable interchangeably [21, 27].

Patients submitted to non-cardiac surgical interventions may also benefit from the improved sensitivity of cTn assays. This setting is associated with relevant cardiovascular morbidity and mortality (with major complications rate varying from 1.7% to 3.5%) [65]. Several potential mechanisms have been recognized to contribute to the pathophysiology of peri-operative AMI, resulting in type 1 or type 2 AMI, or due to stent thrombosis, which is particularly associated with oral anti-platelet therapy interruption [66]. Notably, the pre-operative risk assessment is of great clinical relevance, and over the past decade, cTn elevation has been recognized as a relevant prognostic factor for adverse short- and longer-term outcomes [67]. With the introduction of hsTn, the prognostic value of the marker in these patients has potentially increased according to the capability to detect very minor myocardial damage. A recent study has evaluated if the hsTnT increasing 24 h after surgery could detect peri-operative myocardial damage in patients at high cardiovascular risk undergoing elective non-cardiac surgery [68]. A post-operative myocardial necrosis by hsTnT was identified in 22% of patients (a proportion ~4-fold higher with respect to conventional cTn T assay), even if only 2% of patients experienced clinically apparent AMI. Interestingly, a pre-operative hsTnT elevation, detected in 31% of patients, did not predict peri-operative MI [68]. A larger study has reported that hsTnT measured 7 days prior to surgery outperforms conventional risk algorithms, including clinical variables as well as use of natriuretic peptides, in predicting major adverse events (death, AMI, acute heart failure, and cardiac arrest/resuscitation) [69]. In addition, hsTnT was reported as the strongest independent predictor for the combined endpoint, as patients with concentrations above the 99th percentile cutoff had a 2.6-fold increased risk for the occurrence of one of the defined adverse events [69].

hsTn in stable CAD as a risk biomarker: the “sound of silence”

hsTn has been additionally suggested as a potential screening tool to identify asymptomatic individuals who are at high risk for CVD, both in patients with stable CAD as well as in general population [70]. Particularly, in stable CAD:

- Slightly elevated hsTn concentrations are relatively common (up to a third of patients with computed tomography angiography-documented CAD).
- hsTn elevations are strongly associated with heart failure and cardiovascular death, whereas there is weaker or no association with ischemic events.
- Other mechanisms for release than ischemic injury likely play an important role such as mechanical stress, left ventricular mass, renal dysfunction.

Patients with stable CAD and hsTnT concentrations >18.6 ng/L had a 2.6-fold increased risk for the recurrence of cardiovascular events with respect to those with concentrations <5 ng/L, when monitored during an 8-year follow-up [71]. Similar data have been published for the HOPE cohort, in which subjects with hsTnT concentrations >21 ng/L displayed a 2-fold increased probability for AMI, stroke, or cardiovascular death [72]. Interestingly, an hsTn increase in subjects with stable CAD has been linked to coronary lesion morphology. Patients with non-calcified plaque seem to display higher hsTnT
concentrations vs. those with calcified lesions, and far higher hsTnT concentrations (>21 ng/L) have been characterized in patients with remodeled non-calcified plaque [73]. Because the plaques occurring in these subjects appear to lie in an active “vulnerable” state, one could reasonably speculate on the more likely acute intermittent nature of hsTnT increase with respect to the chronic stable pattern [73].

Limitations

The original clinical data reported in this article are related to our own experience in one academic hospital center. Consequently, the results may be not applicable to other different clinical settings. Furthermore, although we often used the general term “hsTn” in this review, we actually report (and discuss) data obtained in our experience with hsTnT. Because it is known that there can be differences in results found with cTn I and cTn T assays, the clinical data reported in this article cannot be directly applied to cTn I methods [74].

Conclusions

By summarizing the running evidence in the framework of AMI, we can reasonably conclude that hsTn, by markedly improving the analytical performance at low-range marker concentrations, has allowed the safe clinical application of international recommendations (i.e., the 99th percentile limit concept). The impact of the universal definition of AMI has resulted in an increase of this diagnosis by approximately 25%, thus becoming an independent predictor of mortality at 10 years [75].

hsTn have shortened the time to diagnose NSTEMI as well as the observation period of patients with suspected myocardial damage in ED from 9–12 h to 3 h. Fast-track protocols for ruling out and ruling in NSTEMI have been optimized by recommending blood sampling at patient results. ED physicians and cardiologists should be advised that a more diagnostically and cost-effective use of hsTn requires that all clinical variables should be considered in order to increase the pre-test probability of AMI/ACS and that serial hsTn testing be done to detect patients at medium to high risk for AMI/ACS. Importantly, laboratories need to get involved in communicating with clinicians through education, test interpretation, tools, and internal audits of test usage and patient outcomes.

Our experience shows that ED physicians and cardiologists can positively respond to the laboratory’s change in cTn strategy and be satisfied with the education and tools offered by the laboratory specialists.

In frameworks other than spontaneous AMI, the cost-benefit of applying hsTn to critical patients for their risk assessment has recently gained relevance. The capability of accurately detecting very minor cardiac damage appears to contribute more accurate prognostic information and it is expected to improve the survival trends in clinical contexts different from ACS.

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