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Review article
Pregledni članak

DIAGNOSTIC AND PROGNOSTIC INFORMATION PROVIDED BY A HIGH SENSITIVITY ASSAY FOR CARDIAC TROPONIN T

DIJAGNOSTIČKE I PROGNOSTIČKE INFORMACIJE KOJE PRUŽA VEOMA OSETLJIVI TEST ZA SRČANI TROPONIN T

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Summary: Cardiac troponins (cTns) are the preferred biomarkers for the diagnosis of acute myocardial infarction, assessment of risk and prognosis, and for determination of antithrombotic and revascularization strategy in patients with acute coronary syndromes. The implementation of high sensitivity cTn assays into the clinical routine has increased the number of patients diagnosed with myocardial infarction. In addition, the number of patients with elevated cTn levels that cannot be explained by acute ischemic injury was increased, which is observed in patients with chronic heart disease and other nonischemic cardiac injury or in patients with impaired renal function. The new definition of myocardial infarction provides support for the interpretation of elevated cTn measured with high sensitivity cTn assays in patients with suspected acute coronary syndrome. This review will summarize clinical studies with the recently introduced high sensitivity cTnT assay (TnT hs) with reference to recent experience with high sensitivity cTn assays in general.

Keywords: cardiac troponin, high sensitivity cardiac troponin assay, acute myocardial infarction

Kratak sadržaj: Srčani troponini (cTns) preporučuju se kao biomarkeri za dijagnozu akutnog infarkta miokarda, procenu rizika i prognoze, kao i za određivanje antitrombotske terapije i strategije revaskularizacije kod pacijenata sa akutnim koronarnim sindromima. Implementacija visokoosetljivih testova za cTn u kliničkoj praksi je povećala broj pacijenata kod kojih je dijagnostikovan infarkt miokarda. Pored toga, povećan je i broj pacijenata sa povišenim nivoima cTn koji se ne mogu pripisati akutnom ishemijskom oštećenju, što je primećeno kod pacijenata sa hroničnim srčanim bolestima i drugim neishemijskim srčanim oštećenjima ili kod pacijenata sa oštećenom renalnom funkcijom. Nova definicija infarkta miokarda podržava tumačenje povišenih cTn izmerenih pomoću visokoosetljivih testova za cTn kod pacijenata kod kojih se sumnja na akutni koronarni sindrom. Ovde se prikazuju kliničke studije sa nedavno uvedenim visokoosetljivim testom za cTnT (TnT hs) uz uopšteni osvrt na iskustva sa visokoosetljivim cTn testovima.

Ključne reči: srčani troponin, visokoosetljivi test za srčani troponin, akutni infarkt miokarda

Introduction

For more than a decade cardiac cTns I and T have been the preferred biomarkers for the diagnosis of acute myocardial infarction in patients with suspected acute coronary syndromes. The universal definition of myocardial infarction first published in 2000 (1) proposes to use the 99th percentile URL of cardiac cTns in a healthy population for the diagnosis of AMI. It is recommended that cTn at the 99th percentile can be measured with a precision of 10% CV to be able to reliably measure small changes of the analyte at these low analyte levels. Since then there has been a great focus on providing cardiac cTn (cTn) assays with largely improved analytical sensitivity and precision. Recently developed high sensitivity cTn assays are able to detect small amounts of cardiomyocyte injury that could not be detected by earlier versions of the assays. From the increased knowledge gained over the recent years it is now understood that elevated cTns are not necessarily caused by acute ischemic events but also by other clinical conditions. This at first glance appears to be an additional value of the biomarker but has implications on how elevated cTn has to be interpreted in the clinical practice. The intention of the current

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paper is to summarize the clinical performance of the high sensitivity cTnT assay from Roche Diagnostics in recent clinical studies in the context of the current understanding of the clinical information provided by sensitive and high sensitivity cTn assays.

Evolution of cardiac troponin assays

The first biomarkers that were regarded as useful in the assessment of myocardial infarction were enzymatic assays for asparagine aminotransferase (AST) and creatine kinase (CK) and the isoenzyme pattern of lactate dehydrogenase (LDH). These assays suffered from limited sensitivity and specificity. The diagnostic performance was improved with the introduction of enzymatic assays for the more specific MB isoenzyme of CK.

For many years the cTns I and T have been the preferred biomarkers for the diagnosis of myocardial infarction, because of their specificity for cardiac tissue. Studies comparing the diagnostic performance of CK-MB and cTnI or cTnT have demonstrated the superior performance of cTn assays in the identification of patients with acute myocardial infarction (AMI) (3, 4). With further improvement of the diagnostic performance of the cTn assays it could be demonstrated that even small elevations of cTn are helpful in the assessment of short- and long-term risk in patients with acute coronary syndrome (ACS) (5, 6). Cardiac Tn is a useful marker for stratification of patients with ACS for early invasive treatment (5, 7) and for antithrombotic therapy (8–11).

Small amount of cell necrosis can be reliably picked up by high sensitive cTn assays and therefore the assays are regarded as an important tool for the assessment of ischemic injury. This was a major consideration in the redefinition of myocardial infarction published in 2000 (1, 2) where cTns are regarded as the preferred biomarkers for diagnosis of AMI. In the new definition of myocardial infarction the clinical decision limit was set to the 99th percentile upper reference limit (URL) in healthy individuals. As a consequence, even slight elevations of cTn are suspicious for acute myocardial infarction. Results of serial determinations of cTn are an essential criteria in the universal definition of MI. Diagnosis of MI requires a rise or fall in cTn measured in a second or consecutive sample taken after initial presentation. Together with these criteria it was recommended that a cTn assay should have an imprecision of equal or less than 10% CV at the 99th percentile URL. At the introduction of the universal definition none of the commercially available cTn assays was able to fulfill the 10% CV criteria at the 99th percentile. This caused the diagnostic industry to develop more sensitive cTn assays. When the universal definition was applied to conventional cTn assays, the number of patients diagnosed as AMI was increased when the 10% CV decision limit was applied. This number was further increased with the introduction of the sensitive cTn assays into the clinical routine. The development of high sensitivity assays is still ongoing. Several high sensitivity cTn assays have been developed, but are not yet commercially available. The cTnT hs assay is the only assay that is commercially available. By introduction of new detection principles the analytical sensitivity of cTn assays can be further increased. This was demonstrated for the ultrasensitive cTnI assay from Singulex. With this assay the 99th percentile URL was determined at 9 ng/L and the 10% CV limit was observed below 1.6 ng/L (12). Currently, there is no consensus on how to define the analytical sensitivity of cTn assays. One important criterion is the precision at the 99th percentile URL which should be ≤ 10% CV, as recommended by the current guidelines. In addition, the sensitivity of an assay may be defined by the percentage of detectable individuals in a reference population (13). In the paper it is proposed that high sensitivity assays should be able to measure more than 50% of the individuals in the reference population. There is no consensus on how to determine the 10% CV precision limit and the analytical detection limit of cTn assays. In addition, the composition of the reference population has a major impact on the determination of the 99th percentile (13–15). In the absence of standardized protocols for the determination of assay precision, detection limit and the 99th percentile, it is difficult to compare the available information on assay performance of the commercial cTn assays and assays under development with regard to analytical sensitivity (16, 17).

Pathophysiology of troponin release

The pathophysiology of the release of cTn is not completely understood. Although there is sufficient evidence that the release of cTn correlates with cardiomyocyte necrosis in AMI, it is questionable whether the release of cTn is solely explained by cell necrosis. Studies in marathon runners revealed a temporary release of cTn which may not be explained by cardiomyocyte necrosis in analogy to AMI. In contrast to myocardial infarction, the peak levels in marathon runners decrease to the baseline results within 24 h after completion of the run. The underlying pathophysiological mechanism of cTn release in endurance exercise seems to be rather complex, since recent results from an ultra-marathon suggest that individual factors influence the extent and time course in cTn release of individual runners (18). In another study with marathon runners it was observed that runners developed a second peak of cTn release several hours after the end of a marathon run and after cTn had already decreased to baseline levels (19). In analogy to myocardial infarction this observation may be explained by a remodelling process including cell necrosis and/or apoptosis. In a recent

study by Mingels and colleagues (20) with the TnT hs assay it was shown that the median increase of cTnT and I is correlated to the running distance. This indicates that, besides individual factors, the duration of exercise might be a major influencing factor on the release of cTn due to physical stress.

The release of cTn induced by exercise was explained by reversible 'leakage' of myocardial cells and release of cTns from the cytoplasmic pool or, in a second theory, by myocyte necrosis (21). Ultrasensitive cTn assays might be able to detect slight elevations in cTn levels in stress-testing. Recently, Sabatine et al. (22) demonstrated with an ultrasensitive cTnI assay that even small changes in cTnI levels of 1.3 ng/L are strong predictors of inducible myocardial ischemia with an odds ratio of 3.54 (95% CI: 1.42 to 8.80). Elevated levels of cTn in patients with chronic heart disease are explained with remodelling including apoptosis. The elevated risk of patients with chronic heart failure supports the theory of underlying irreversible pathological processes. However, reversible release of cTn in analogy to the marathon runners may also contribute to the elevated cTn levels in these patients (23).

Technical features and performance of the TnT hs assay

The high sensitivity cardiac troponin T assay (TnT hs) from Roche Diagnostics uses the monoclonal mouse antibodies of the third and fourth generation of the cTnT assay. In the new version of the assay the detection antibody was genetically reengineered by replacing the constant C1 regions of the mouse antibody by C1 regions of human IgG. This modification of the detection antibody was introduced to further limit the binding to heterophilic antibodies. The 10% CV limit was determined below 13 ng/L in an evaluation at 8 study sites (24, 25). The limit was calculated from the intermediate (within site) or total precision in measurements from 63 or 84 aliquots of human serum and plasma pools performed over 21 days, with 4 repetitions of the assay calibration. The measurements were done on 4 different types of analyzers and included two reagent lots (25). The assay has a limit of detection or limit of blank (LoB) of 3 ng/L determined in an analyte-free serum based calibration material (24). A precommercial version of the TnT hs assay was used in early clinical studies with the new assay. This assay had the final formulation of the TnT hs assay but a preliminary standardization. More recent studies used the commercial assay with the final standardization. In the majority of studies the performance of the high sensitive cTnT assay was compared to the performance of the 4th generation cTnT assay from Roche Diagnostics with a limit of detection at 10 ng/L, 10% CV limit at 30 ng/L and a 99th percentile below 10 ng/L.

The search for the right reference population – Definition of the 99th percentile URL

The upper reference limit for cTn and CK-MB assays is defined by the 99th percentile in a healthy reference population (1). Recently developed high sensitivity cTn assays enabled – for the first time – determination of cTn levels in the majority of healthy individuals (12, 25–27). This ability of high sensitivity cTn assays has a major impact on the clinical application of the marker, especially in risk assessment, where even rather low cTn levels provide prognostic information (6, 28). Recently it was suggested to define the sensitivity of a cTn assay by the percentage of individuals in a reference population that can be detected above the detection limit (13). Initial reference studies were done with a precommercial version of the high sensitivity cTnT assay and included 616 apparently healthy individuals recruited at two sites and 1318 blood donors recruited at one site in Europe (24, 26). A third reference study was done as part of the multicenter evaluation trial of the final version of the TnT hs assay (25). For the reference part of the trial 533 apparently healthy individuals were recruited at 7 study sites. The sites were located in Europe, Asia and the US. The health status of the volunteers, aged between 20 and 71 years, was checked by a questionnaire and lab testing of defined parameters. The results for the 99th percentile were 13.5 and 13.2 ng/L in the studies with the precommercial assay mentioned above and 14.2 ng/L in the study with the final version of the assay with the final standardization. Another study with the precommercial assay by Mingels et al. (29) produced a slightly higher value for the 99th percentile at 16 ng/L.

All studies in apparently healthy individuals showed statistically significant differences in the values of males and females and an increase of cTn values by age. Similar trends were observed in a study with the Siemens TnI Ultra assay (30). In contrast, no differences between women and men were observed in a study with a precommercial high sensitivity assay from Beckman (27). The implication of lower reference values in women for the diagnostic assessment in clinical routine has not been discussed yet, despite the fact that sex-specific reference values appear to be useful, especially in the prediction of cardiac risk. Due to the correlation of cTn with age and sex, the composition of the reference population has a significant impact on the calculation of the 99th percentile. Apart from that, it has to be taken into account that subclinical or asymptomatic heart disease may contribute to higher cTn levels in apparently healthy individuals. This can be concluded from population-based studies (14, 15, 31) and from a recently published study that showed that cTn even at levels below the 99th percentile of the TnT hs assay predicts poorer prognosis in patients with stable cardiovas-

cular disease (32). For this reason, it cannot be ruled out that the current reference studies with the TnT hs assay included a number of patients with subclinical heart disease. Because the prevalence of subclinical heart disease increases with age, it was suggested to determine the 99th percentile in a well characterized population of young healthy individuals (13). This approach may not be helpful for the routine use of high sensitive assays in the ED because it will cause a further increase in the number of patients with small dynamic changes in cTn. More clinical studies with high sensitivity cTn assays are needed to evaluate the clinical relevance of small changes at low cTn levels with regard to patient outcome.

Implications for cTnT hs testing for the diagnosis of MI

For many years the measurements of cardiac cTns have been integrated into the triage of patients in the ER with suspected acute coronary syndrome. The importance and acceptance of cTn is reflected in recent guidelines, where cTns are proposed as the preferred cardiac biomarkers in the diagnosis of acute myocardial infarction (1, 33). In addition to diagnosis, risk prediction became more prominent with the introduction of cTn assays with increased sensitivity and had significant impact on the clinical decision making in the ER. The use of ROC optimized cut-offs at relatively high cTn levels is not any longer recommended because of the short-term risk in patients observed at rather low cTn levels. Even small elevations in cTn levels above the detection limit of conventional cTn assays identify high-risk patients that benefit from early invasive treatment (5).

Problems caused by the use of high sensitivity cTn assays in clinical practice

Because of the clinical relevance of slightly elevated cTn levels, the universal definition of myocardial infarction includes the URL (99th percentile) in the rationale for the assessment of acute ischemic injury. However, this recommendation causes a substantial increase in the number of patients presenting with elevated cTn but without further evidence of AMI. For better differentiation of patients with AMI from patients with other cardiac injury, the criteria of rise or fall of cTn in consecutive blood samples were included in the universal definition of MI. This concept should allow to distinguish acute cardiac injury from chronic cardiac injury. However, the universal definition does not define how the fall and rise criteria can be transferred into clinical practice. For the differentiation of ischemic injury in patients with ACS from chronic cardiac injury (as in end stage renal disease), the National Academy of Clinical Biochemistry (NACB) recommends a 20% change in the follow-up sample to the presentation sample (34). The suggested change in cTn values was derived from the 10% CV criteria for imprecision of cTn assays at the 99th percentile URL. In addition, the biological variation (inter- and intra-individual) has to be taken into account (35). When % change criteria in follow-up samples are applied, the number of falsely diagnosed AMI cases, which were indicated by measurements with sensitive cTn assays, can be substantially reduced. Recently, Apple and colleagues (36) demonstrated that a specificity of >90% can be achieved with a sensitive cTnI assay by using a 30% change criterion when the follow-up sample was taken between 4 and 12 hours after the presentation sample. Unfortunately, the application of the 30% criterion had a negative effect on the sensitivity (< 80%). In contrast, a study by Giannitsis and colleagues (37) showed that a 20% change criterion in cTnT did not improve specificity above 60% in ACS patients including patients with evolving non-ST-segment-elevation myocardial infarction (NSTEMI) when the cTnT hs assay was used for the measurements. In this study, cTnT changes with optimal results for specificity required relatively large changes of 117% and 243% for the period of 3 and 6 hours from presentation, respectively. In addition, the sensitivity for the diagnosis of MI was significantly decreased to < 80% when the high cTn criterion was applied. In another study, where patients with suspected ACS were studied, more than 45% of patients that fulfilled a criterion of 20% were finally not diagnosed as AMI (38). The majority of patients not diagnosed with myocardial infarction had diagnoses related to cardiac disease and were more frequently readmitted for suspected ACS. The 20 or 30% change criteria are especially problematic for patients with a presentation cTn sample close to the 99th URL, as the translation of the 20 or 30% criteria in absolute changes is reflected in a small absolute increase or decrease in cTn (3 to 4 ng/L with the TnT hs assay) in the consecutive sample. Thus the, relatively low change criteria may be regarded as not sufficient for the patients with low levels of cTn at presentation. Alternatively, a step algorithm would help to overcome this problem by using larger criteria in the low cTn range, as proposed by Giannitsis and White for the TnT hs assay (39, 40). Apart from the discussed problem to define appropriate change criteria, it should be taken into account that elevated cTn levels are observed in other etiologies than acute ischemic injury caused by vascular occlusion (1, 2, 41, 42). Therefore, for the interpretation of changes in cTn values it, is crucial to interpret the information by the biomarker in the context of the clinical presentation of the patient.

Benefits of high sensitivity cTnT testing in clinical practice

The greatest benefit of high sensitive cTn assays is the early assessment of patients with AMI. Studies show that already at admission the more sensitive assays can identify the majority of patients with the final diagnosis for AMI at cTn levels above the 99th

percentile URL (43, 44). In a recent study with patients presenting with ischemic chest pain, Reichlin et al. (45) observed that the high sensitivity cTnT assay detected 95% of the patients with the final diagnosis of MI above the 99th percentile URL at 14 ng/L already at presentation. In contrast, the conventional 4th generation cTnT assay detected only 72% of these patients above the 10% CV limit of 30 ng/L. As indicated above, the use of the low decision limit at 14 ng/L does negatively affect the specificity, which was observed to be 80%. However, the low specificity might partially be explained by the use of conventional cTn assays for gold standard diagnosis. Another important result was that the high sensitivity cTnT assay together with sensitive cTnI assays are able to detect elevated cTn levels within 2 to 3 hours from the onset of pain. With patients who presented within 3 hours from the onset of chest pain the diagnostic accuracy of the cTnT hs assay was already high, with an area under the receiver-operating-characteristic curve (AUC) of 0.92, compared to an AUC of 0.76 obtained with the conventional 4th generation cTnT assay. Cardiac TnT measured with the high sensitivity assay did clearly outperform myoglobin with an AUC of 0.79. At the 99th percentile URL of 14 ng/L the TnT hs assay had a negative predictive value of 99%. Most likely the increased sensitivity of cTn assays will help to shorten the time to decision in the ER in the long run. However, more studies are required to establish applicable criteria for the differentiation between acute myocardial injury caused by ischemia and other clinical conditions of myocardial injury.

Implications of the TnT hs assay for the diagnostic groups NSTEMI and unstable angina pectoris

Since the introduction of the first cTn assays the sensitivity was continuously improved with the consequences that more and more patients were diagnosed as NSTEMI who with the earlier generation assays would have been diagnosed as unstable angina pectoris (UAP) or patients with clinical symptoms of ischemia at rest without dynamic changes in the cardiac biomarker. The new definition of MI considers clinically relevant elevations of cTn starting at above the 99th percentile URL. High sensitivity cTn assays detect dynamic changes in serial samples at cTn levels below the detection limits of the less sensitive conventional cTn assays. In a recent study, where the cTnT hs assay and the earlier generation of the TnT assay (4th generation cTn T) were used, the number of patients with the final diagnosis of UAP was decreased by the hs TnT assay by 20% and the number of NSTEMI was increased accordingly (24). With a precommercial ultra-sensitive cTn I assay Wilson et al. (46) demonstrated that the majority of patients diagnosed as UAP with a conventional cTn assay developed cTn values above the 99th percentile (2.8 ng/L) within 8 hrs from presentation. The percentage of patients with elevated cTn values was 44% at presentation and 82% at 8 hours after presentation. It was concluded that the majority of patients with ischemic chest pain at rest have detectable myocardial injury.

Elevated cTn levels in stable coronary artery disease

A high percentage of apparently healthy individuals can be detected within the assay range of high sensitivity cTn assays, which could not be achieved with the conventional assays. Cardiac TnT levels below the 99th percentile URL are already associated with increased risk for cardiac events in patients with stable coronary artery disease. This was shown in a study with patients with stable angina pectoris and preserved left ventricular function (32). In contrast to studies in patients with ACS (7) slightly elevated cTnT did not predict reinfarction. Slightly elevated cTn results correlated with cardiovascular morbidity and all causes of death and worsening of heart failure.

Cardiac troponin testing in chronic heart failure

Heart failure (HF) is one of the major health problems in the Western World. With increasing life expectation heart failure will become even more prominent. Highly specific cardiac biomarkers are expected to provide meaningful support in therapy monitoring and diagnosis. B-type natriuretic peptides (BNP and NT-proBNP) are currently regarded as the most potential markers. Recently, Latini and colleagues (47) demonstrated that cTnT is an independent risk marker in patients with stable chronic heart failure. Even small elevations of cTnT measured by the high sensitivity cardiac troponin T assay in the Valsartan Heart Failure Trial (Val-HeFT) predicted poor outcome or progression of the disease. Cardiac TnT measured by the high sensitivity TnT assay was an independent risk marker in multivariate analysis including clinical risk factors and BNP. In this analysis the 4th generation cTnT assay did not improve risk prediction. The study demonstrated that cTns are independent risk predictors in chronic heart failure which provide incremental prognostic information to B-type natriuretic peptides. Population based studies have provided evidence that even conventional cTn assays can predict risk for development of chronic heart disease eventually by identification of patients with subclinical or early stages of heart dysfunction among asymptomatic patients. This has not been yet demonstrated for the TnT hs, but it is assumed that high sensitivity Tn assays may be even more effective in the prediction of individuals who will develop heart failure (14, 15, 31).

Cardiac troponin T in renal disease

There is emerging evidence that increases in cTnT in asymptomatic patients with end stage renal disease (ESRD) indicates subclinical myocardial necrosis or injury (48). Studies with ESRD patients have shown that elevated cTnT levels are predictive of cardiac risk in these patients. The lower incidence of cTnI elevations has led to the initial suggestion that cTnI may be a more specific diagnostic and prognostic marker than cTnT in reflecting myocardial injury in patients with renal failure (49, 50). However, the Global Use of Strategies to Open Occluded Coronary Arteries IV (GUSTO IV) trial, which includes patients with suspected ACS, indicates that elevated cTnT levels are strongly predictive of poor short-term prognosis independent of creatinine clearance (51). Whether the introduction of more sensitive cTnI assays enables the use of cTnI for risk prediction in ESRD is still a matter of debate. Contraindicative studies have been published (52). In a recent study with haemodialysis patients it was demonstrated that the high sensitivity cTnT assay identifies more patients with elevated cTn levels compared to a sensitive cTnI assay and the 4th generation cTnT assay (53). All haemodialysis patients had elevated cTn T values above the 99th percentile when measured with the high sensitivity cTnT assay. Individual patients showed significant increases of cTn in serial measurements over 6 months, which most likely indicates an increasing cardiac risk. On the other hand, more than half of the patients showed only low variations in cTn values which might be explained by more stable cardiovascular disease. In summary, the variation of cTn in the patients with and without history of cardiovascular disease was rather low (total CV 17% and 14%, respectively). In another recent study in haemodialysis dependent patients with chronic renal failure, cTnT measured with the TnT hs assay was the most powerful biomarker for prediction of all-cause death compared to age, CRP, NT-proBNP, and albumin (54).

Conclusion

The high sensitivity cTnT assay allows earlier diagnosis of MI and has the potential to help shorten the time to decision for further treatment/triage of the patients. Nevertheless, the assay is currently challenging the ED physicians by the increased number of patients with elevated cTn results that are not related to an acute ischemic condition. The observation of a falling or rising pattern in cTn is important to distinguish acute ischemic from chronic, non-ischemic conditions. The clinical presentation and the patient history are often the key for the interpretation of the cTn values and dynamic and therefore play a major role in the diagnosis of AMI. Additional studies are required to evaluate and validate an appropriate algorithm including the criteria for fall and rise of cTn to assist ER physicians in finding the right diagnosis. This especially applies for the safe diagnosis of patients, whose clinical presentation is hard to define and whose history is difficult to bring to light in the emergency setting.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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