Conference Paper

How to Use High-Sensitivity Cardiac Troponins in Acute Cardiac Care?

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High-sensitivity troponin assays, when used and viewed in the clinical context, provide a definite diagnostic benefit compared to conventional troponin assays, especially due to the improved early rule-out of acute myocardial infarction in troponin-negative patients. The interpretation of positive troponin results and, thus, the rule-in of acute myocardial infarction have become more challenging. High sensitivity Tn assays can detect very small but prognostically significant troponin increases, but the underlying diagnoses are diverse. Especially patients with non-ACS-related troponin elevations have an adverse outcome and require careful patient management. Additionally, the interpretation of a significant rise or fall of troponin values has not been standardized yet. Despite these challenges, troponin is a unique marker, which allows for the specific detection of myocardial cell necrosis and the new high sensitivity assays are a great chance to identify more patients at risk and improve their management and care.

1. Introduction

The introduction of high sensitivity troponin assays has made the interpretation of troponin results in clinical practice much more challenging.

This paper briefly describes the analytical characteristics of the new high sensitivity troponin assays and discusses their use for the early diagnosis of non-ST-elevation myocardial infarction (NSTEMI), their prognostic value and implications for the differentiation of NSTEMI and non-ACS myocardial injury, and other causes of troponin elevations.

2. Analytical Characteristics of High Sensitivity Troponin Assays

The high sensitivity troponin T assay has a sensitivity of 3 ng/L. In order to understand the full meaning of this, it is helpful to imagine pouring 1 kg of sugar into Lake Zug in Switzerland, which has a volume of $3.18 \times 10^{12}$ L. If 50 μL of this lake water was analyzed with a comparable high sensitivity assay, it would be possible to detect sugar in the lake water. As a consequence, patients with very small myocardial injuries, independent of the underlying cause, have measurable troponin levels, and interpretation of troponin results in the context of the clinical setting is now more important than ever.

3. Early Diagnosis of NSTEMI

High sensitivity assays detect troponin elevations in over 50% of patients with suspected myocardial infarction already at admission; in patients who present late after symptom onset, this rate is even higher (around 70%). Thus, early after admission, hsTn assays have a much higher diagnostic accuracy than conventional troponin assays. More importantly, hs troponin assays enable us to exclude acute myocardial infarction much earlier than conventional troponin assays. Keller et al. were able to show that the negative predictive
value for the exclusion of AMI at 3 h after admission is almost 100% [1]. Biener et al. confirmed these findings in a study comparing a 3-hour versus a 6-hour protocol for the diagnosis of NSTEMI in 459 patients. For the rule-out of non-STEMI, the negative predictive values of the hsTnT assay were 94.9% at admission, 98.7% at 3 hours, and 100% at 6 hours with comparable performances at 3 and 6 h (Figure 1) [2]. The early rule-out of AMI can be further improved by combining troponin with copeptin [3].

In summary, patients presenting with acute chest pain who test negative for troponin measured with an hs assay at admission and again at 3 hours, without a high-risk profile and without typical symptoms, can be discharged home and have an excellent outcome.

Patients presenting with acute chest pain are classified as patients with the working diagnosis acute coronary syndrome (ACS) purely based on their symptoms [4]. The next step in the diagnostic work-up is the ECG, dividing patients into ST-elevation MI and non-ST-elevation ACS. In STEMI, biomarkers have no diagnostic function at admission but can be useful in specific situations later.

3.1. Troponin-Delta. The differentiation between NSTEMI and unstable angina or non-ACS requires serial troponin measurement. The important question in this context is the definition of a significant change of troponin levels between the first measurement at admission and subsequent measurements 3 or 6 hours later. The literature reports different cutoffs for a significant troponin delta. The NACB initially proposed a ≥20% difference [5]. Apple et al. postulated a ≥30% increase between admission and 6 h after admission for the VITROS cTnlT [6], and Wu proposed an ≥46% increase or 32% decrease to exceed the biological variation [7]. Recently, a preliminary report from Heidelberg hospital experience with TnT-hs suggested a ≥100% (doubling concentration) at 3 h (Giannitsis and Katus—white paper available upon demand). A proposal for a ≥3 standard deviation change will be published soon (Thygesen, Mair, Katus, Plebani, Giannitsis, Lindahl, Hasin, Galvani, Tubaro, Alpert, Per Venge, Collinson, Biasucci, Koenig, Mueller, Hubert, Hamm, and Jaffe; the study group on biomarkers in cardiology of the ESC working group on Acute cardiac care; principles for the application of troponins in acute cardiac care; expert consensus document; submitted to publication).

Thygesen et al. recently developed a flow chart to clarify the diagnostic stratification [8]. Due to this flow chart, patients presenting with chest pain and a troponin below the URL at admission should be diagnosed with AMI if their troponin after 3 or 6 h increases above the URL or at least by ≥50% of the URL. In patients already presenting with a positive troponin value, an increase of over 20% is required to diagnose AMI.

4. Prognostic Value of hsTn

It is important to note that even the detection of small increases of troponin has a prognostic impact. Weber et al. analyzed the diagnostic and prognostic potential of the high-sensitive troponin T assay and compared these results with those of a contemporary troponin T assay in the Bad Nauheim ACS (patients with evident ACS) and the prognosis in acute coronary syndrome (PACS) registry (patients with general chest pain). They were able to show that hsTnT provided independent prognostic power for mortality within 6 months in both cohorts, which was superior to that of the contemporary TnT assay. Kaplan-Meier survival analysis revealed that hsTnT with a value >14 pg/mL was associated with a significantly increased mortality rate [9]. This was especially interesting in the PACS cohort where a high number of patients were troponin negative when using the conventional Tn assay. Thus, hs TnT showed an incremental prognostic value, allowing for improved risk stratification also in patients with negative conventional troponin T levels at admission.

Mills et al. evaluated whether lowering the diagnostic threshold for myocardial infarction (MI) with a sensitive troponin assay could improve clinical outcomes. In a retrospective analysis, they observed that patients with intermediate troponin values between 0.05 and 0.19 ng/mL had a higher mortality than patients with troponin values above 0.20 ng/mL. As a consequence, a new troponin cutoff of 0.05 ng/mL was implemented, resulting in a significant reduction in mortality for patients with intermediate troponin values [10]. The explanation for this phenomenon was that patients with intermediate troponin values were now recognized as patients with cardiac events and were, thus, receiving appropriate care.

In summary, it is very important to recognize that even minimal troponin increases are associated with an adverse outcome and that these patients require appropriate therapy.
5. Troponin Elevations Caused by Diseases Other Than ACS

In a recently published study at the Chest Pain Unit in Heidelberg, of 3,327 patients who were admitted to the CPU, 20% were troponin positive, but 69% of these troponin elevations were not due to an ACS [11]. McFalls et al. identified all hospitalized patients in 2006 who were tested for troponin during their initial reference hospitalization and categorized them on the basis of their ICD-9 code into acute coronary syndrome or nonacute coronary syndrome. Of all patients with elevated troponin levels, 57.2% had non-ACS conditions. Interestingly, mortality after 1 year in patients with a nonacute coronary syndrome condition was higher than in patients with acute coronary syndrome [12].

This is a big challenge for the treating physicians, because standard therapeutic strategies for these patients are not available. There are many reasons why troponin values can be increased (Table 1). It is extremely important to classify patients on the basis of their underlying diseases, because patients with non-ACS-related troponin elevations may have a worse prognosis than patients with ACS. Most of these patients are severely ill and require intensive care and treatment.

6. Discussion

For the management of patients with suspected ACS in the Emergency Department, early rule out of AMI is extremely useful. The exclusion of AMI gives us time for a thorough workup of patients without feeling rushed into invasive diagnostics.

The rule-in of AMI has become more challenging with the introduction of high sensitivity assays. On the other hand, when troponin was discovered more than 20 years ago, the initial paper was rejected for fear that physicians might be too confused by the concept and the flood of positive troponin results. The introduction of the new assays poses a very similar situation to the first introduction of the biomarker, as it will lead to the identification of a larger number of patients with positive results and especially positive results in patients without myocardial ischemia. Up to now, nobody really knows how to treat these patients and how to correctly estimate their risk. It is an enormous challenge for the next years to really understand these patients, but it will be extremely worthwhile as these are high-risk patients who will profit from intensified patient care.

Thus, positive results carry a fascination which needs to be solved in the future, while the negative predictive value provides us with an excellent tool to guide patient care.

Another challenge is the correct interpretation of a rise or fall in troponin levels, the troponin delta. It is likely that this issue will not be solved in the way of a standard delta value but will always be a balance between sensitivity and specificity. The most important factor is to understand that there is a problem in all patients with increased troponin levels. Whether there is a kinetic rise or fall or whether the patient has a small myocardial infarction is of secondary importance, especially as patients do not require urgent catheterization and can undergo further diagnostics.

All patients with a positive troponin result should undergo thorough diagnostic workup. This includes patients with known, chronically increased troponin levels, for example, with heart failure or ischemic heart disease combined with a chronic kidney disease. These patients have to be regarded as high-risk patients and require intensive monitoring and should, also in an ambulant setting, be seen more regularly.

7. Conclusions

With high sensitivity troponin assays even very small areas of myocardial necrosis can be detected. This provides cardiologists with the unique advantage of a highly specific marker of myocardial cell death.

We gain this advantage with an increased number of patients where the underlying cause and, more importantly, the appropriate therapeutic strategy are yet unclear. When using high sensitivity troponin assays, it is, more than ever, important to use the results in the context of the patient’s individual clinical setting.

Table 1: Underlying diagnoses in non-ACS patients with increased troponin values.

<table>
<thead>
<tr>
<th>Underlying diseases in patients with increased troponin levels</th>
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<tbody>
<tr>
<td>Cardiac contusion, including ablation, pacing, cardioversion, or endomyocardial biopsy</td>
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<tr>
<td>Congestive heart failure-acute and chronic</td>
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<tr>
<td>Aortic dissection, aortic valve disease, or hypertrophic cardiomyopathy</td>
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<tr>
<td>Tachy- or bradyarrhythmia, or heart block</td>
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<tr>
<td>Apical ballooning syndrome (TakoTsubo cardiomyopathy)</td>
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<td>Rhabdomyolysis with cardiac injury</td>
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<td>Pulmonary embolism, severe pulmonary hypertension</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Acute neurological disease including stroke, or subarachnoidal hemorrhage</td>
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<td>Infiltrative diseases, for example, amyloidosis, hemochromatosis, sarcoidiosis, and scleroderma</td>
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<tr>
<td>Inflammatory diseases, for example, myocarditis, or myocardial extension of endo/pericarditis</td>
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<tr>
<td>Drug toxicity, for example, adriamycin, 5-fluorouracil, herceptin, and snake venom</td>
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<tr>
<td>Critically ill patients, especially with respiratory failure, or sepsis</td>
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<td>Burns, especially if affecting &gt; 30% of body surface area</td>
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References


