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Review

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Laboratory diagnostics of myocardial infarction – troponins and beyond

Abstract

In the case of suspected acute coronary syndrome and myocardial infarction positive diagnosis or exclusion strongly depend on the use of biomarkers and in particular cardiac troponins (cTn). Especially in the early phase of myocardial infarction the sensitivity of cTn assays has been unsatisfactory. This has led to the investigation of many other potential markers for the early diagnosis of myocardial infarction. In addition, several traditional markers have been advocated, e.g., myoglobin, as these were considered to be more sensitive than cTn. With the advent of high-sensitive (hs) cTn assays the value and practical use of the alternative or additional markers has to be reassessed. According to the currently available data, no single marker is superior to hs-cTn for the diagnosis of acute myocardial infarction. In particular, the notion of superior sensitivity of myoglobin compared to cTn no longer holds true. There are two protein markers, heart-type fatty acid binding protein and copeptin, and plasma free fatty acids that may increase the diagnostic value and specifically the negative predictive value when determined on admission in combination with hs-cTn. However, the incremental gain, if any, is small. Further data are needed to determine, whether these markers can in fact improve diagnosis and if they are superior to the recommended use of the relative or absolute change of hs-cTn after 3 h.

Keywords: acute coronary syndrome; biomarkers; high sensitive cardiac troponin; myocardial infarction.

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Introduction

The diagnosis of acute myocardial infarction (MI) and acute coronary syndromes (ACS) remains an issue of much interest in medicine, because these entities constitute the most common potentially life-threatening diagnoses in an emergency department and are amenable to effective treatment if diagnosed correctly and in a timely fashion. The diagnosis of MI has depended for years on clinical presentation and electrocardiographic patterns. The availability of sensitive and in particular highly specific biomarkers of myocardial damage, such as the cardiac troponins (cTn) has led to a conceptual change in the definition and diagnosis of myocardial infarction in the second half of the 1990s [1–3]. As a result the combination of symptoms and an increase above the reference limit in these specific biomarkers, preferably cardiac troponin were considered as diagnostic for MI [4, 5].

In the acute setting diagnosis relies on biomarkers, if the electrocardiogram is not conclusive. This is clearly the case for all patients with non-cardiac chest pain in whom the diagnosis of MI and ACS has to be ruled out, but also for many patients with unstable angina or non-ST-elevation myocardial infarction. Therefore, guidelines for the appropriate diagnosis and treatment in these cases have been issued and are regularly updated by the American and European professional associations [6, 7].

One limitation of the assays for cTn was their limited analytical sensitivity [8]. Thus, the first generations of these assays were not able to reliably quantify the low concentration of cTn in plasma from healthy persons. This situation has significantly improved with the advent of more sensitive cTn assays in recent years. Large clinical studies have shown that these assays can improve the diagnostic work-up of patients with acute chest pain and suspected MI [9–11]. This has already induced changes in the guidelines for diagnosis of MI [6]. At present we have not reached the end of this development. In fact, some of the tests used in the current studies do not fulfil the proposed requirements of high sensitivity, which require that at least 50% of healthy individuals should have a measurable cTn serum/plasma concentration, i.e., cTn above the limit of detection of the assay. Furthermore, the coefficient of variation at the 99th percentile of the distribution should be <10% [12]. The current status of the available assays has been reviewed recently [13].

The advent of high sensitive (hs) cTn assays raise several questions regarding the definition of myocardial infarction, rule-in and rule-out of myocardial infarction, as well as when and how to treat patients with increased cTn concentrations according to the hs-cTn assays. A major point is the increased analytical and diagnostic sensitivity of the assays and its impact on the diagnosis and definition of MI. These issues have been amply reviewed and discussed in the literature, recently [6, 14–16]. They are therefore not the topic of this short review.

Another interesting question relates to the role of other biomarkers in the diagnosis of myocardial infarction or the acute coronary syndrome. Many biomarkers of myocardial damage have been proposed and used in the past, because it was apparent that the conventional cTn assays did not perform ideally. Are these markers obsolete now or can they still improve diagnosis based on hs-cTn? This question has been asked in the past for several of the traditional MI-markers, e.g., lactate dehydrogenase or creatinine kinase-MB activity which have been abandoned largely by now. In addition, to markers of ischemia and necrosis, several novel non-specific biomarkers have been identified in recent years that might add diagnostic information in the setting of suspected acute coronary syndrome or myocardial infarction.

The use of alternative markers has been reviewed in detail previously [17]. However, most of the studies evaluated in this review neither compared the alternative markers with cTn nor assessed the potential added value. Furthermore, hs-cTn assays were not evaluated at all limiting the relevance of these older studies.

As indicated above, all these known and novel alternative biomarkers can be divided into two groups. Group 1 are biomarkers related to myocardial damage or necrosis. They are more or less specific for myocardial tissue and are released into the circulation during ischemia and/or necrosis of myocardium and/or other tissues. The second group constitutes biomarkers related to the response of the body to acute stress or injury. These markers are non-specific for myocardial damage, but may be highly sensitive in combination with a specific marker of myocardial damage. In Table 1 the relevant biomarkers are summarized. While the markers indicating myocardial damage all have been investigated for their potential to substitute for cTn, the non-specific stress markers have mostly been used in combination with cTn trying to improve early diagnosis of myocardial infarction. It should be noted that many biomarkers have been tested for their prognostic potential in the past, e.g., brain natriuretic peptide. While these markers may be included in the therapeutic decision-making in the future, they are not specific for MI and therefore of limited value in making the diagnosis of MI. Therefore, these markers are also not in the focus of this short review.

Biomarkers indicating myocardial damage
Myoglobin
Creatine kinase MB (CK-MB)
Glycogen phosphorylase BB (GPBB)
Fatty acid binding protein – heart type (hFABP)
Ischemia modified albumin (IMA)
Free fatty acids (FFA)
Biomarkers indicating general stress/damage
Copeptin
C-reactive protein
Myeloperoxidase
Neopterin

Table 1 Alternative or complementary biomarkers for the diagnosis of myocardial infarction.

Myoglobin

Myoglobin is a low molecular (17 kDa) cytosolic protein of striated muscle. It is able to bind oxygen and serves as an oxygen reservoir for the muscle cell in cases of increased demand. Myoglobin is rapidly liberated into the extracellular space during muscular damage or necrosis. As myoglobin is present in skeletal muscle, its use in the diagnosis of MI has been limited by the low specificity for myocardial damage. Nevertheless myoglobin has been regarded as the most sensitive biomarker of myocardial damage in the past. In fact, high diagnostic sensitivity is still reported as the major strength of myoglobin in a recent guideline [7]. Even some recent studies adding myoglobin to conventional cTn suggest an improved diagnostic value [18].

With the advent of more sensitive cTn assays this view must be revised and studies using conventional cTn assays as comparison should no longer be performed. In a large cohort we showed that a more sensitive assay (TnI-Ultra, Siemens) had a higher sensitivity than myoglobin even in the group of patients who presented <3 h after the onset of chest pain (84% vs. 62%). It should be noted that this TnI assay does not yet fulfil the criteria of high sensitivity (see above) [10]. This result could be confirmed and extended using a true high sensitivity assay (Architect STAT high sensitive troponin I assay, Abbott Diagnostics). Even 2 h after the onset of chest pain myoglobin did not provide higher diagnostic sensitivity than the hs-cTnI assay. Accordingly, it is not surprising that the addition of myoglobin to hs-cTnI did not improve the diagnostic

performance of hs-cTnI alone [19]. These data are in line with several other studies comparing the value of myoglobin with hs-cTn [20, 21]. In summary, the supposed higher sensitivity of myoglobin for the early diagnosis of myocardial infarction does not hold in times of hs-TnI assays. Therefore, the use of myoglobin in this setting is at least questionable.

Creatine kinase MB (CK-MB)

CK-MB has been used for decades in the diagnosis of MI. While the early tests were based on enzyme activity, CK-MB mass is currently measured by various ligand binding assays. There is now ample evidence that CK-MB mass determination is inferior to conventional cTn so that its use has not been advocated any more before the advent of hs-cTn. In fact, guidelines recommend CK-MB only, if cTn is not available [6, 7]. Thus, for the diagnosis of acute MI in the setting of an emergency room or chest pain unit, CK-MB cannot be recommended. However, due to the prolonged elevation of cTn after an acute MI, CK-MB may be of value in the setting of suspected reinfarction or after cardiac surgery.

Glycogen phosphorylase BB (GPBB)

Glycogen phosphorylase is an enzyme involved in cellular glycogen metabolism. It is associated with glycogen in the sarcoplasmatic reticulum as a homodimer of approximately 97 kDa. Glycogen phosphorylase catalyzes the initial step of glycogen degradation, There are three isoforms B, M, and L which are present in brain and heart (B), muscle including myocardium (M), and liver (L). The BB homodimer has been evaluated for its ability to improve the diagnosis of MI. Myocardial ischemia increases the degradation of glycogen. Under these conditions glycogen phosphorylase is released from glycogen and part of it reaches the extracellular space and the circulation. Initial small clinical studies suggested a high sensitivity for the early detection of MI with a comparably good specificity [22]. However, in a recent analysis in a large cohort, GPBB was clearly inferior to contemporary and hs-cTnI. Also in the subgroup of patients with <3 h of chest pain GPBB was significantly inferior to hs-cTnI. The addition of GPBB to hs-cTnI did not lead to a significant increase in the area under the receiver operator characteristics (ROC) [19]. The difference to the previous studies may be related to the much higher cut-off for the 99th percentile determined in this study and the fact that some of the previous studies were not sufficiently powered or designed to determine specificity.

In summary, GPBB has a limited sensitivity and specificity for MI and does not add to the diagnostic information obtained by hs-cTnI. Interestingly, recent data suggest that elevated GPBB may add prognostic information beyond hs-cTnI and brain natriuretic peptide (BNP) [23]. Whether this is of clinical value in terms of therapeutic stratification needs to be determined.

Heart type fatty acid binding protein (H-FABP)

H-FABP belongs to the family of fatty acid binding proteins. It is a 15 kDa cytosolic protein. H-FABP is present in very high concentration (approx. 5 mg/g tissue) in myocardial tissue. However, it is not absolutely specific for myocardial tissue and is also present in lower concentration in skeletal muscle, kidney, and brain. Due to its small size, H-FABP is rapidly cleared from the blood by the kidney. H-FABP has been widely analyzed for its potential in the diagnosis of MI [17]. Most studies suggest that the diagnostic performance of H-FABP is comparable to the conventional cTn assays. Thorough comparisons to contemporary sensitive or hs-cTnI have been performed only in the recent past. One study in a large cohort shows that the diagnostic performance of H-FABP as determined by ROC analysis is inferior to hs-cTnI in the diagnosis of acute MI [19]. This is true for all patients as well as the subgroup presenting within 3 h of chest pain onset. Interestingly, H-FABP appeared to improve the diagnostic value of hs-cTnI slightly in this study. Thus, addition of H-FABP to hs-cTnI leads to a small but statistically significant increase in the area under the curve in ROC-analysis. This increase is less than that associated with the addition of the change in hs-cTnI after 3 h, however, it is available at admission of the patient. Similar conclusions have been reached by other groups [21]. The potential of H-FABP to improve early diagnosis of MI deserves further analysis. At present, it appears too early for a final conclusion.

Ischemia modified albumin (IMA)

As the name implies, albumin is modified under ischemic conditions. While the underlying mechanism is not absolutely clear, there are data suggesting that free radicals,

low pH, or an increase in free fatty acids may be instrumental [15]. As a consequence the amino terminal part of albumin loses its capacity to bind transition metals, e.g., cobalt or nickel. The binding capacity for cobalt can be determined colorimetrically. It should be noted that the modification of albumin and therefore the determination of IMA is not specific for myocardial ischemia. Many studies have been performed to assess the diagnostic value of IMA in the work-up of patients with suspected MI [17, 24]. Most of them show that IMA is not specific enough to serve as a single biomarker for MI. However, its use in combination with cTn has been advocated and IMA has been approved by the FDA to rule out MI in combination with the ECG and cTn. A recent study in a group of patients with suspected ACS in which 12.5% had unstable angina and only 7% had acute MI, IMA was inferior to cTn and did not add any additional information if used in combination with cTn [25]. This is of particular relevance, because IMA is supposed to increase with ischemia alone and should therefore be more sensitive than markers of necrosis in a cohort with unstable angina. Thus, overall IMA must be regarded as obsolete as long as no further data are available with IMA and hs-cTn.

Free fatty acids (FFA)

FFA in plasma have been shown to increase during myocardial ischemia. Their role in diagnosis of acute MI is not yet well established. This is in part related to the fact that quite different methods have been used to quantify FFA as a whole, individual FFA, or to analyze FFA acid patterns qualitatively [15, 25]. Evaluation in combination with hs-cTn is scarce to date. One study using a novel method comparing FFA patterns suggests an improved diagnostic value when hs-cTn is combined with FFA [25]. It should be kept in mind that this study had a relatively high percentage of patients with unstable angina compared to MI. The gain in diagnostic power was for the combined ACS population.

Copeptin

Copeptin is part of pro-arginin-vasopressin (proAVP) and is released in equimolar fashion during cleavage of the active hormone AVP from the propeptide. Production of the antidiuretic AVP is rapidly induced by states of the circulation that require retention of water, e.g., hypovolemia, hypotension, or hyperosmolarity. AVP and consequently copeptin are produced in states of circulatory stress, such as MI. While it is obvious that increased copeptin production is not specific for MI, it is potentially a sensitive marker due to the rapid response to changes in the circulatory state. Therefore, it has been hypothesized that copeptin might complement specific biomarkers of MI in the early diagnosis of MI. Several groups have investigated this in the recent past. The data indicate that copeptin might indeed improve early diagnosis of MI.

Reichlin et al. [26] showed in a cohort of 492 patients with chest pain onset within the last 12 h that the combination of copeptin with a conventional cTnT assay increased the negative predictive value (NPV) to almost 100% in patients with cTnT below the diagnostic cut-off. In their study the combined determination of cTnT and copeptin at admission resulted in a NPV of 99.7% with a threshold of copeptin at 14 pmol/L. This procedure would have correctly excluded MI in approximately two-thirds of the cohort with only one false-negative patient.

Keller et al. [27] showed in a cohort of 1386 patients that determination of copeptin at admission improved the early rule-out of MI in combination with a conventional cTnT assay by increasing the negative predictive value significantly from 88.5% for cTnT alone to 95.8% for the combination (using the 95th percentile of copeptin as cut-off). A comparable increase in NPV was observed independent of the onset of chest pain before admission to the emergency room. Due to the poor specificity of copeptin the positive predictive value of the combination was poor, so that the addition of copeptin to the diagnostic work-up only improved rule-out of MI. It should be noted that copeptin was still able to increase the NPV in combination with a contemporary sensitive cTnI assay from 95% to 99% in the group of patients presenting within 3 h from the onset of chest pain. While the NPV was not quite as good as in the Reichlin study, the potential of copeptin for rule out of MI was confirmed. Several other studies with conventional cTn assays support the conclusions of the two studies. Again the NPV is increased, but does not reach 100% [28, 29].

Using a truly hs-cTnI assay Keller et al. observed in a later study a marginal but significant improvement of the NPV when copeptin determination was performed in addition to hs-cTnI at admission [19]. Again the NPV of the combination of hs-cTnI and copeptin at admission was significantly different from 100%. It should be noted though that the addition of the delta change of hs-cTnI after 3 h increased the area under the curve in ROC-analysis more than the addition of copeptin to the diagnostic workup. Giannitsis et al. also showed an improvement of the NPV with the addition of copeptin to the determination of hs-cTnT in 503 patients with suspected MI [30]. Potocki

et al. using a hs-cTnT assay in combination with copeptin observed only a non-significant trend for an improvement of the diagnostic value when the two assays were used together [31]. Karakas et al. saw no diagnostic improvement by adding copeptin to hs-cTnT in a study involving 366 patients [32]. It is not clear why these four studies showed different results regarding the role of copeptin. One reason might be the proportion of patients with definite MI in the studies. This was higher in the two studies with a statistically significant improvement by addition of copeptin (>20%) than in the study with a positive trend (18%) or no significant improvement (<5%). Furthermore, one should not forget that the incremental diagnostic gain provided by copeptin was small in the positive studies.

Thus, while the potential of copeptin to improve early rule-out of MI has been well documented with conventional cTn assays, the role of copeptin and the optimal strategy for the workup of patients with suspected acute MI in times of hs-cTn assays still needs to be defined.

Myeloperoxidase (MPO)

MPO has been advocated as a biomarker suitable for the diagnosis or risk stratification in patients with suspected acute coronary syndrome. However, a recent study showed no added value of MPO determination for the diagnosis of MI [33]. As other markers of inflammation it may still have a role in assessing the risk of future events.

C-reactive protein (CRP), neopterin

Both markers are indicative of an inflammatory or acute phase reaction. They have no value in the diagnosis of acute MI in the emergency room situation [34], but are clearly related to the risk of future cardiovascular events.

Conclusions

The major finding of recent clinical studies with hs-cTn assays is the fact that the diagnostic value of these tests is significantly higher than that of the conventional cTn assays. In particular the sensitivity in the first 3 h increased dramatically. This has consequences for the use of alternative or complementary diagnostic laboratory tests for MI. Current data suggest that some of the assays that had been shown to be potentially superior to conventional cTn assays definitely lose their advantage. This is true for, e.g., myoglobin, which is not more sensitive than the hs-cTn assays no matter how long the patient had been symptomatic before the blood test. Another example is copeptin that had been shown to add diagnostic information to the conventional cTn assays. With the novel hs-cTn assays the incremental gain is apparently minor if it exists at all. It should be noted that these considerations apply to the early diagnosis of MI, not to the prognostic stratification.

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