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Review Article

Cardiac enzyme in emergency medicine

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Abstract

Acute chest pain is an important and frequently occurring symptom in patients. Chest pain is often a sign of ischemic heart disease. Chest pain due to suspected Acute Coronary Syndrome (ACS) is responsible for a large and increasing number of hospital attendances and admissions. Current practice for suspected ACS involves troponin testing 10–12 hours after symptom onset to diagnose Myocardial Infarction (MI). Patients with a negative troponin can be investigated further with Computed Tomographic Coronary Angiography (CTCA) or exercise Electrocardiography (ECG). A review of cardiac biomarkers as screening test in acute chest pain over 15 years was conducted. Separate searches were under taken for biomarkers. We Searched electronic databases up to 2004-2014, reviewed citation lists and contacted experts to identify diagnostic and prognostic studies comparing a relevant index test (biomarker, CTCA or exercise ECG) to the appropriate reference standard. We classified studies to two part early rise biomarkers, high sensitivity biomarkers.

Conclusion: Although presentation troponin has suboptimal sensitivity, measurement of a 10-hour troponin level is unlikely to be cost-effective in most scenarios compared with a high sensitivity presentation troponin. Measurement of cardiac troponin using a sensitive method was the best test for the early diagnosis of an Acute Myocardial Infarction (AMI). Measurement of myoglobin or Creatine Kinase-MB (CK-MB) in addition to a sensitive troponin test is not recommended. Heart-type Fatty Acid-Binding Protein (H-FABP) shows promise as an early marker and requires further study.

Keywords: Risk factor, Acute myocardial infarction, Emergency department, Troponin

Introduction

Every year, over 1.5 million patients are admitted to hospitals after presenting to the Emergency Department (ED) with acute chest pain. Only a small percentage of these admitted patients have Acute Coronary Syndromes (ACSs) and the vast majority of them are discharged with non-cardiac diagnoses. Acute chest pain is an important and frequently occurring symptom in patients. Chest pain is often a sign of ischemic heart disease, although gender, age, and comorbidity may modify how acute Coronary Heart Disease (CHD) presents itself within the individual patient. Acute chest pain may indicate a potentially life-threatening situation, but it is also commonly acknowledged that a wide variety of differential diagnosis exists, many with lower health impacts and less serious potential effects (1).

Chest pain caused by ACS is an important factor in increasing the number of hospitalizations. So it is necessary to weight the costs and benefits of accurate diagnosis to determine the optimal strategy for MI diagnosis (2).

After establishing Myocardial Infarction (MI), then the risk of future adverse events can be determined using biomarkers of ischemia or inflammation, exercise Electrocardiography (ECG) or Computed Tomographic Coronary Angiography (CTCA), along with antithrombotic treatment or coronary intervention which are used to reduce the risk of adverse outcomes in individuals with positive tests (2). ACS is usually associated with chest pain and must be differentiated from other common causes of chest pain such as muscular pain, gastro-oesophageal pain and anxiety. As clinical assessment is unreliable and the electrocardiogram may be normal in the presence ofA CS, establishing such differentiation is difficult. Patients with suspected ACS constitute a large and varied population; many of them have not ACS or CAD, but have non-cardiac causes for their chest pain. So ACS and Coronary Artery Disease (CAD) must be carefully identified to establish the best interventions (3). Determining the optimal strategy involves weighing the benefits of reducing adverse events against costs of additional investigation

and treatment (4).

Methods

A review of cardiac biomarkers as screening test in acute chest pain over 15 years was conducted. Separate searches were done for biomarkers too. We searched electronic databases from 2000 up to 2014, reviewed citation lists, and contacted experts to identify diagnostic and prognostic studies comparing a relevant index test (biomarker, CTCA or exercise ECG) to the appropriate reference standard [MI according the universal definition, CAD on Invasive Coronary Angiography (ICA) or Major Adverse Cardiac Events (MACE)] in patients presenting with suspected ACS. We classified studies into two parts. They encompass early rise biomarkers, and high sensitivity biomarkers.

Early risk biomarkers

Many systematic reviews have been conducted to investigate the diagnostic (5) and prognostic (6) accuracy of troponin testing in suspected ACS (7). Other systematic reviews also are done to determine the diagnostic accuracy of troponin, CK, CK-MB, and myoglobin (8). The result shows that troponin has the highest accuracy for MI. The standard diagnostic method for suspected ACS is to measure troponin levels 10-12 hours after symptoms onset. There are alternative and effective biomarkers to improve the diagnostic accuracy of troponin assay for MI and it forms the reference standard (4). However; alternative biomarkers may have a role in targeting two limitations in troponin measurement (2). First, because of the limited early sensitivity of troponin, there is a potential for biomarkers with better early sensitivity for MI and care improvement. Second, although a negative 10-12-hour troponin assay stratifies patient to a low risk of adverse outcome, this does not equate to a negligible risk. Thus alternative biomarkers can have an important role in determining the further risk of patients. The relative insensitivity of the early generation of cardiac troponin assays indicates that much information can be provided about patients with acute chest pain by exploring the small cytoplasmic proteins which leak trough the ischemic myocardial cell membrane. Myoglobin, a single–chain globular protein, could be an early marker for MI. It is consisted of a haem prosthetic group and is the primary oxygen storage protein in muscle tissues (2).

Finding markers that are realized when myocardial ischemia occurs, is an alternative approach. A form of human serum albumin is ischemia-modified albumin, in which ischemia has an effect on N-terminal amino acids in order to bind transition metals. Fatty acid-binding proteins are relatively small proteins, of 126-137 amino acids in length. These proteins are present in tissues such as heart, intestine, and liver that have active fatty acid metabolism. Heart-type Fatty Acid-Binding Protein (H-FABP), a myocardial isoform, is predominantly in heart. However; it has been seen in other tissues such as skeletal muscles and distal tubal cells of the kidney (2).

Myoglobin

Myoglobin (with molecular weight of 16.7 KDa) is a single-chain globular protein that consists of a haem prosthetic group. Myoglobin is the primary Oxygen-carrying pigment in muscle tissues. It is also found in cytoplasm and considering its low molecular weight, it can be released earlier than other cytoplasmic biomarkers after myocyte necrosis. In some studies it is proposed that myoglobin measures can be an early marker for AMI (9-11). Comparing Myoglobin measures with kinetics and cardiospecificity of other markers has shown that myoglobin measurement can be used in combined with other cardiac biomarkers in a panel for early diagnosis of AMI (12-14), especially in point of care testing (15).

Creatine kinase MB isoenzyme

Creatine Kinase-MB (CK-MB) isoenzyme is the more cardiac-specific isoenzyme of CK and is present in the cytoplasm and forms 5-50% of the CK of the myocardium, which is one of the earliest cardiac biomarkers used for the biochemical detection of an AMI (16-18). Mass assays which are designed and developed for CK-MB are automated and form the basis of current methodology (19-21). One of the most established biomarkers of AMI is the measurement of CK-MB mass and is still recognized in the universal definition of MI. The advantage of this method is an earlier rise of CK-MB, compared to cardiac troponin (22).

Fatty Acid-binding Protein (FABP) and other early phase reactive protein

FABPs are relatively small proteins (15 DKa) that consist of 126-137 amino acids. These proteins are present in tissues such as heart, liver, and intestine which have an active fatty acid metabolism. They reversibly bind long chain fatty acids so can enhance their intracellular translocation. Nine types of FABP have been identified, each has a specific pattern of tissue distribution and their intracellular half-time is 2-3 days (23). H-FABP, an isoform of myocardial, is found predominantly in the heart, but also is present in other tissues such as skeletal muscle and the distal tubal cells in the kidney. The potential role of H-FABP in diagnosing the MI has been investigated by a number of studies (24-26). H-FABP may be an early cytoplasmic marker of myocardial ischemia and myocardial injury (2). Other markers of the atherothrombotic process, in addition to the measurement of cardiac troponin, can be measured and allow earlier diagnose. Markers of atheromatous plaque destabilization or rupture have been proposed, including inflammatory markers [C-Reactive Protein (CRP), interleukin 6, interleukin 33/ST2 and Growth Differentiation Factor 15 (GDF-15)] and biomarkers that are considered to be associated with the plaque itself [Myeloperoxidase (MPO), matrix metalloproteinases

and Pregnancy-Associated Plasma Protein A (PAPP-A)]. Markers of myocardial dysfunction such as B-type natriuretic peptide (BNP) N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), copeptin and adrenomedullin also can be used alternatively. A systematic review of 22 novel biomarkers such as CRP, MOP, BNP and H-FABP (8) has shown that the evidences to support the usefulness of these biomarkers in ED assessment of suspected ACS are insufficient. Along with this analysis, further studies have been conducted to estimate the diagnostic and prognostic accuracy of alternative biomarkers. However; other researches have shown that modern troponin assays have much improved the early sensitivity. Thus; the aim of this study is to investigate the role of early biomarkers in identifying MI before 10-12 hours, and the role of alternative biomarkers in providing additional risk stratification for troponin-negative patients with suspected ACS (2).

High-sensitivity troponin and alternative biomarkers

The cardiac troponins from part of the cardiac contractile apparatus, the troponin–tropomyosin complex, and comprise three troponins [troponin C, troponin I (TnI) and troponin T (TnT)] plus tropomyosin (1-30).

Some immunoassays have been developed to measure TnT and TnI, as they have unique structures. Preliminary studies have demonstrated that the measurement of cardiac troponin is both more sensitive and more specific for myocardial injury than biomarkers used previously. TnT or TnI is now the recommended biomarkers for MI. The original redefinition of acute MI suggested that the analytical imprecision of the assay should allow measurement with a low analytical imprecision within the reference interval of the assay. This quality specification is not met by the assays available in the past years and this causes to increasing improvement in assay quality until current generation of sensitive troponin assays has been formed. Sensitive troponin assays can measure troponin in healthy individuals with a high degree of analytical imprecision, typically <10% imprecision at the 99% of a reference population (1-30).

In addition to meeting the quality specification stipulated in the universal definition of acute MI, the new sensitive assays can detect myocardial injury substantially earlier than the previous generation of assays. Progressive improvement in the analytical performance in troponin assays has demonstrated that, the analytical performance of second—and third generation assays—is already beginning to outstrip other markers of myocardial injury such as myoglobin and CK-MB (27,28). Also, studies on new high-sensitivity assays have demonstrated that they are superior to all of the conventional markers of myocardial injury.

Troponin

The two main subjects that will be discussed in this section are as follows:

1) The use of troponin and other biomarkers to diagnose MI when hospitalization.

2) The use of other biomarkers, exercise ECG and CTCA to risk-stratify patients with acute chest pain and a negative troponin.

Troponin should be measured at least 10-12 hours after the onset of symptoms using the 99 high risk of a diagnostic threshold. It can be helpful in diagnosing MI accurately and identifying patients with high risk of adverse outcome. It also helps patients benefit from hospital treatment. However, patients waiting for delayed testing are currently detained in hospital until 10-12 hours after symptoms onset (29). This delay results in additional health services costs and causes inconvenience for patients. An earlier diagnostic assessment could allow earlier hospital discharge, thus decreasing costs, but would risk missed MI opportunity to benefit from treatment if sensitivity were suboptimal. High-sensitivity troponin assays, either alone or in combination with other biomarkers, can be used to diagnose MI before 10-12 hours. But the cost savings of this approach must be weighted against the missed benefit, in other words, the additional benefits of 10-12 hours troponin sampling need to be weighted against the additional costs (2). Considering that the risk is not negligible, it will be beneficial to measure other biomarkers that can predict increased risk independent of troponin levels. Troponin-negative patients may also be investigated by exercise ECG or CTCA for identifying those with CAD and the patients with an increased risk of adverse outcome may benefit from coronary intervention and medical treatment. So, there is a necessity to estimate the diagnostic accuracy of exercise ECG and CTCA for CAD, and the prognostic accuracy of exercise ECG and CTCA for MACEs and the cost effectiveness of using exercise ECG or CTCA in selecting patients who need hospitalization (1-30).

Description of diagnostic studies of presentation troponin

Diagnostic studies of presentation TnI and TnT have been identified in this research. Two studies that evaluated TnI and TnT, applied variable inclusion and exclusion criteria and in several studies patients with a diagnostic ECG were excluded. Prevalence of MI varies from 5–73% and was relatively high (2), suggesting that patients cohort may have been affected by implicit selection processes. Time delay from symptoms to presentation varies from 1.2 (mean) hours to 6 hours (median). Data showed that several studies have used different diagnostic thresholds for the index test; however, the data in this study is based on the 99th percentile, 10% Coefficient of Variation (CV) and Limit of Detection (LoD). In all of these studies, the universal definition of MI was used as the reference standard and in most of them some form of adjunction was also used – taking into account the results of tropinin testing. In most cases, the troponin used for the reference standard was a standard (i.e. not high sensitivity) assay using

the 10% CV or 99th percentile as a diagnostic threshold. However, in Christ *et al* study a reference standard based on High-sensitivity TnT (HsTnT) alongside a reference standard based on the standard assay was used (30). The data in this study is collected based on the standard assay reference standard. The studies were generally high quality, and the lower-quality studies were excluded by our selection criteria. Presentation troponin measurement is obviously not independent of a troponin-based reference standard, so the focus in the assessment of verification bias is on whether or not the index and reference standard troponin were measured on different samples. There is some uncertainty about whether index and reference standard tests were assessed blind or not. This is unlikely to have an influence on reporting the index test as in most cases this is done by a mechanized process producing a quantitative result (1-30).

Description of diagnostic studies of other biomarkers

Diagnostic studies of other biomarkers have been identified in this study too. The prevalence of MI was lower than the studies of troponin, H-FABP and myoglobin, and varied from 5% to 29%. The median time from symptom onset to sampling varied from 2 to 4.5 hours. Most of the studies used a modern troponin assay with an acceptable threshold for the reference standard (2).

Diagnostic studies of biomarkers in combination with troponin: some studies have compared the analyses of the sensitivity and specificity of biomarkers in combination with troponin alone. We did not use any meta-analysis in our research as no combination was evaluated (2).

Troponin and the alternative biomarker are combined and classified as positive if either test is positive. However, the combination is classified as positive only if both tests are positive. Thus, in most studies the combination had higher sensitivity and lower specificity than troponin alone, whereas the combinations tested had lower sensitivity and higher specificity than troponin alone (1-29). The results of these studies suggested that combining troponin with another biomarker at presentation, with elevation of either biomarker producing a positive test, results in significantly improved sensitivity but with a loss in specificity that can be substantial. In none of these analyses a high-sensitivity troponin assay was used. The results of the troponin meta-analysis indicated that a similar enhancement in sensitivity at the expense of specificity can be achieved if a lower threshold for troponin positivity is used (29).

Diagnostic accuracy of presentation biomarkers for MI

A large number of studies have estimated the accuracy of troponin at presentation for diagnosing MI, compared with a reference standard based on the universal definition using delayed troponin testing. The accuracy of troponin at presentation for diagnosing MI has been estimated in a large number of studies and the results were compared either a reference standard that is based on the universal definition using delayed troponin testing. In many of these studies the troponin assay, used as the index or reference standard, was inadequate and also, because of the threshold, comparing and synthesizing data from different studies was difficult (1-30).

The differences in estimates of sensitivity and specificity for different assays indicate that there are differences in study methods and populations, however one can conclude that using a lower threshold for positivity and high-sensitivity assay can improve sensitivity at the expense of specificity. It is unknown that whether the loss of specificity indicates the expected loss of specificity, as seen where the threshold for positivity is lowered for an imperfect test, or whether the apparent False-Positives (FPs) may indeed be True-Positives (TPs), which are misclassified by an inadequate reference standard. Further data provided in this study can help to determine whether the estimates of sensitivity for troponin at presentation are lower when compared with a high-sensitivity reference standard. The results of this study suggest that high-sensitivity assays have sufficient sensitivity at presentation to identify most cases of MI that would subsequently be identified by a standard 10-hour troponin test, but these estimates are not completely reliable and a significant proportion with MI will be missed by presentation troponin testing. Conducting 10-hour troponin testing mostly depends on the costs and benefits of detecting additional cases and it can be explored in detail in the economic analysis (1-30).

Conclusion

Increasing use of high-sensitivity troponin assays results in many advantages and facilities service provision. More positive results can be obtained by high-sensitivity assays than standard assays, but the prognostic significance of these additional positive cases is not clearly known. Some Services are provided, considering the hypothesis that patients with a positive troponin have an increased risk of adverse outcome and further investigation and intervention will be useful for these groups. This assumption may not be applicable for some patients in which their troponin elevation has a small increase or shows no significant increase in risk. Widespread use of high-sensitivity troponin testing can be potent to significantly increase demand for cardiology services. However further research is needed to determine how and whether this demand should be met (1-29). (Early rise biomarker with low sensitivity).

Test for the early diagnosis of an AMI is the measurement of cardiac troponin by using a sensitive method. Although diagnosis 90 minutes from admission was safe but 100% diagnostic sensitivity was not obtained at that time point and more research is necessary to determine the optimal earliest time point when an acceptable diagnostic sensitivity can be achieved. We do not suggest measuring myoglobin or CK-MB as well as a sensitive troponin test. H-FABP is promising in terms of an early marker and needs more study. The measurement of copeptin is

not recommended as a routine test in patients presenting with acute chest pain. Ten-hour troponin testing seems to be cost-effective in comparison to rapid rule-out strategies only if patients can be discharged as soon as a negative result is available (29).

Ethical issues

Not applicable.

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