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Copeptin as Emerging Marker for Myocardial Infarction

Manisha Naithani*

Assistant professor, Department of Biochemistry, AIIMS, Rishikesh.

ABSTRACT

Myocardial infarction is the largest manifestation of Coronary artery disease. Coronary heart disease is the single largest cause of increasing disease burden and is one of the leading causes of death in developing countries. Acute Myocardial Infarction is not only widely prevalent but it is also notoriously time consuming to diagnose and prognosticate. Troponin is the preferred biomarker for the detection of myocardial necrosis and is a Class I indication for the diagnosis of Myocardial Infarction. Considering the limitations of Troponin, the quest for a perfect marker continues. Some like Copeptin, which have shown promise, have been a hub of much debate and interest. In the past years, since the development of Copeptin assay, it has been studied as a diagnostic and prognostic marker in different diseases. In the present paper we will focus our discussion on the utility of testing Copeptin in Acute Myocardial Infarction to assess its clinical role and validation of its use.
Keywords: Myocardial infarction, Biomarker, Cardiac Troponin and Copeptin.

*Corresponding author

INTRODUCTION

Myocardial Infarction: the magnitude of problem

Myocardial infarction [MI] describes the process of myocardial cell death due to ischemia, or the perfusion imbalance between supply and demand within the coronary arteries as a result of an acute thrombotic process. Myocardial infarction is the largest manifestation of Coronary artery disease. Coronary heart disease [CHD] is the single largest cause of increasing disease burden [1] and is one of the leading causes of death in developing countries. Three-fourths of global deaths due to CHD occur in the low and middle-income countries. The CHD death rate, however, varies dramatically across the developing countries with varying incidence, prevalence, and mortality rates reflecting the different levels of risk factors, other competing causes of death, availability of resources to combat CHD, and the stage of epidemiologic transition that each country or region finds itself. Incidence of CHD has declined appreciably in the developed countries [3]. Despite the declines CHD remains the leading cause of death in the UK [3], the USA, and other wealthy countries [2]. Thus to combat the CHD epidemic emerging in the developing world is a priority.

Coronary heart disease [CHD] is the single largest cause of death in the developed countries and is one of the leading causes of disease burden in developing countries as well. CHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. According to data from National Health and Nutrition Examination Survey 2007–2010, the overall prevalence for MI is 2.9% in US adults ≥20 years of age. MI prevalence is 4.2% for men and 1.7% for women. Projections show that by 2030, prevalence of CHD will increase ≈18% from 2013 estimates [4].

Diagnostic difficulties of MI

Acute Myocardial Infarction [AMI] is not only widely prevalent but it is also notoriously time consuming to diagnose and prognosticate. Rapid assessment of these patients is critical to direct further diagnostic and therapeutic strategies. The diagnostic cornerstones and test complementing clinical assessment in current AMI guidelines are Electrocardiography [ECG] and cardiac troponin [5, 6]. They allow for diagnosis of AMI within the first 3 h after presentation of patients in the Emergency department [7] and offer the opportunity to initiate appropriate, treatment [8,9].The vast majority of these patients with suspected AMI, however, finally prove not to have AMI [10]. Thus current rule out method of AMI is time-consuming and expensive [11].

One-quarter to one-third of patients with AMI present without significant ECG changes indicative of acute ischemia; therefore, ECG is of little help to rule out AMI [10, 12].

Another baffling factor is non Q wave MI. In a recent study the absolute numbers, prevalence and incidence of unrecognized Q-wave MIs has been found to be low [13], but the prevalence and incidence of recognized MI in the same study is also low, therefore a notable

proportion of all detected MIs were unrecognized Q-wave MIs. 33% of prevalent MIs and 25% of incident MIs were unrecognized Q-wave MIs [13]. There can be conditions confounding the ECG diagnosis of AMI. ECG abnormalities that mimic myocardial ischemia or MI are numerous. Pre-excitation, obstructive, dilated or stress cardiomyopathy, cardiac amyloidosis, Left Bundle Branch Block, left anterior hemiblock, Left Venticular Hypertrophy, right ventricular hypertrophy, myocarditis, acute cor pulmonale, or hyperkalemia may be associated with Q waves or QS complexes in the absence of MI [14].

Biomarkers: a perfect solution

The outcome of patients after AMI has improved with advances in medical therapy, but still it remains a leading cause of morbidity and mortality. Risk stratification at an early stage after AMI remains important and may be useful in helping to select treatment regimens in the future. Clinical features may be useful for predicting patients who are at risk of developing complications after AMI, but they lack sensitivity and specificity. Biomarkers are emerging as a useful tool for predicting prognosis in patients. Biochemical marker testing has revolutionized the approach to diagnosis and management of Myocardial infarction.

The earliest biomarkers employed in the detection of ischemia included aspartate aminotransferase, total lactate dehydrogenase, and its isoenzymes [15]. However, these biomarkers are no longer used since they have a wide tissue distribution limiting the specificity for myocardial necrosis. The next generation of cardiac biomarkers included creatine kinase [16], its isoenzyme Creatine kinase MB [CK -MB]. However, CK-MB also constitutes 1%–3% of the creatine kinase in skeletal muscle and is present in a small fraction in other organs such as the small bowel, uterus, prostate, and diaphragm [17]. Therefore, the specificity of CK-MB can be reduced in the setting of major injury to these organs, especially skeletal muscle. When compared to CK-MB and other cardiac biomarkers, troponin [I or T] has demonstrated nearly absolute myocardial tissue specificity as well as high clinical sensitivity for myocardial ischemia [18, 19] Thus, with the development and clinical availability of troponin assays [cTnT], troponin has largely supplanted CK-MB for the initial detection of MI. Troponin is the preferred biomarker for the detection of myocardial necrosis and is a Class I indication for the diagnosis of MI [20]. B-type natriuretic peptide and its more stable counterpart, N-terminal pro-B-type natriuretic peptide [NTproBNP], covering a range of acute coronary syndromes [21]. There has been many more biomarkers like heart fatty acid binding protein, glycogen phosphorylase-BB, NT-pro-brain natriuretic peptide, D-dimer, high sensitivity C-reactive protein, myeloperoxidase, matrix metalloproteinase- 9, pregnancy associated plasma protein-A, soluble CD40 ligand claiming to detect myocardial ischemia earlier have not demonstrated an added benefit with the exception of heart fatty acid binding protein, compared with the measurement of cardiac troponin alone [22].

Limitations of Troponin

Firstly, despite extensive research and evolving diagnostic technology, patients with symptoms possibly resulting from an acute coronary syndrome usually undergo investigation

for at least 6 hours [and often longer] before AMI can be excluded confidently [23, 24]. The major limitation of current troponin assays is a sensitivity deficit at presentation due to a delayed increase of circulating levels [25]. Prolonged monitoring over 6 to 9 h and serial blood sampling is required for exclusion of AMI. Most patients [74% to 88%] admitted to Emergency Department of hospitals, making up more than one-quarter of acute medical admissions. Only minority of these [approximately 25%] ultimately are diagnosed with an acute coronary syndrome, and many fewer are diagnosed with AMI [26, 27, 28].This contributes to overcrowding in the Emergency Department, and a hike in associated costs [29, 30].

Secondly, serum biomarkers of myocardial necrosis should be used with caution since there can be alternative, non-thrombotic mechanisms of troponin elevation. The diagnosis of myocardial infarction should be reached at when both biomarkers are detected and the clinical setting is consistent with myocardial ischemia. Many disease states can be associated with an increase in cardiac biomarkers in the absence of AMI. These elevations arise from pathologic mechanisms other than thrombotic coronary artery occlusion, and require treatment of the underlying cause rather than the administration of antithrombotic and antiplatelet agents [31, 32]

Alternative, non-thrombotic causes and mechanisms of troponin elevation include tachycardia, heart failure, infiltrative disorders, myocarditis, sepsis, anemia, pulmonary embolus, intracranial hemorrhage, stroke, drug toxicity, and renal failure. Thirdly, false positive troponin elevations can occur due to hemolysis and assay interference with heterophilic antibodies [33]. It is estimated that heterophilic antibodies cause about one false result in every 2000 investigations with modern immunoassays [34]. To minimize the occurrence of false positive troponins, non-specific blocking antibodies have been added to modern assays to reduce interference with the results [34].

Apart from these, although the exact mechanism of troponin elimination is unknown, given its relatively large molecular size, troponin is believed to be cleared by the reticuloendothelial system [35]. However; recent evidence suggests that troponin T is fragmented into molecules small enough to be renally excreted, which may explain the high prevalence of troponin T elevation in patients with renal failure [36]. High-sensitivity assays for both troponin T and I are commercially available and are beginning to come into clinical use. Advances in immunoassay technology have resulted in multiple second-generation troponin I assays and a fourth generation troponin T assay, with a fifth-generation assay in development. The troponin T assays are produced by a single manufacturer, making results comparable. In contrast, there are several methodologies employed in troponin I assays across many manufacturers, and a lack of calibrator standardization has resulted in significant variation in troponin I results among different assays [37]. Re infarctions cannot be detected using Troponins, though these are common complication of AMI within first week since the levels remain elevated for long. The rapid and reliable rule out of AMI, therefore, represents one of the largest unmet needs in clinical medicine.

Copeptin: an alternate to existing markers

These drawbacks has made it essential that the answers should be sought elsewhere, hence the need of research and path breaking trials using other markers to meet with multiple challenges when applied in the clinical setting. One biomarker which is generating a lot of interest and speculation is Copeptin, the C- terminal end of pro vasopressin [a precursor of arginine vasopressin]. The arginine-vasopressin system plays a crucial role in the regulation of the individual endogenous stress response [38].

It is released from the hypothalamus in response to changes in plasma osmolality and arterial hypovolaemia. In general, AVP plasma values are increased in patients with chronic heart failure [39] and recent studies also point towards similar increase in AMI. Arginine vasopressin or anti diuretic hormone is a nonapeptide, synthesized within the magno cellular neurons of the hypothalamic supraoptic nuclei and paraventricular nuclei. It is transported along their axons to the posterior pituitary for storage before ultimate release into the blood stream.

AVP contributes to osmoregulation and cardiovascular homeostasis and it may have a role in cardiopulmonary resuscitation [40]. Vasopressin is synthesized as part of a 166-amino acid long precursor protein called preprovasopressin. It consists of a signal peptide, AVP, neurophysin II, and Copeptin [41]. This preprohormone is cleaved as it is transported along the axon [42]. The C-terminal end of provasopressin is a 39- amino acid glycopeptides present in serum [43] with a leucine-rich core segment [44,45]. It has been suggested that the function of Copeptin is to help in the folding of the vasopressin precursor which, in the absence of this glycopeptide, is less stable [46].The diagnostic use of AVP has been described in various disorders like heart failure and septic shock [47]. There are concerns about the validity of measurement of AVP in plasma, because it is known to be unstable in isolated plasma, even when stored at -20 C [48]. AVP binds to platelet and is rapidly cleared from plasma [49]. Investigation of the role of the vasopressin was thus hampered by the instability of this peptide. Copeptin has emerged as an alternate in the same clinical settings since it is secreted in equimolar amounts to vasopressin [50]. This glycopeptide is stable for days after blood withdrawal and can be quickly and easily measured.

Gene & structure

Vasopressin gene is located in chromosome 20 [p13][51]. The gene is composed of three exons: the first exon encodes the nonapeptide, the second exon encodes the central portion of the neurophysin II, and the third exon encodes the C-terminal part of the preprohormone, Copeptin. The structure of Copeptin has recently been characterized with size-exclusion chromatography and found to have a molecular mass around 5 kDa[52].

Method of estimation of Copeptin

Currently Copeptin is measured with a sandwich immunoassay [53]. It uses two purified sheep polyclonal antibodies to the C-terminal region. Antibody raised against a peptide representing amino acids 132 to 147 of prepro AVP is bound to polystyrene tubes, while other antibody raised against a peptide representing amino acids 149 to 164 of prepro AVP is labelled with methyl acridinium N- hydroxysuccinimide ester and used as tracer, for chemiluminescence detection. The assay requires 50 µl serum or plasma and yields results within 3 hours. The analyte shows ex vivo stability for at least 7 days at room temperature and for 14 days at 4°C.

Normal Copeptin levels

The median Copeptin level in 359 healthy individuals was found to be 4.2pmol/l [53]. Copeptin showed a relatively broad distribution in healthy individuals 1.0 –13.8 pmol/L. This distribution is similar to that reported by Robertson et al [54] for AVP. Stratification according to sex and age revealed lower values in females [men, 5.2 pmol/L, women, 3.7 pmol/L] but there was no major difference in median Copeptin concentrations after stratification according to age groups.

Applicability of Copeptin as a marker in diseases of infectious and non infectious variety

In the past years Copeptin has been studied as a diagnostic and prognostic marker in different diseases. As a diagnostic marker Copeptin has been evaluated in patients with diabetes insipidus, it offers an alternative to the laborious and ambiguous water deprivation test [55]. As a prognostic marker, Copeptin levels were found to be independent predictors of survival in critically ill patients suffering from hemorrhagic and septic shock [56], community- acquired pneumonia [57], and acute exacerbations of chronic obstructive pulmonary disease [58].

Copeptin levels also have prognostic implications in diseases of non infectious aetiology, foremost example being heart failure. Studies have been conducted assessing use of Copeptin as a marker in heart failure. They inferred that Copeptin is an excellent predictor of outcome in advanced heart failure patients, its value being superior to that of BNP [59, 60]. Neuhold et al [2008] reported that Copeptin levels were found to escalate with New York Heart Association [NYHA] Functional class. In patients with NYHA functional classes II and III, Copeptin was not only found to be most potent single predictor of mortality but was superior to BNP or NT proBNP [61]. Studies have pointed out that prognostic information provided by Copeptin provided prognostic information independent of natriuretic peptides [62, 63].

Copeptin in Myocardial infarction

Huge interest has been evoked by the possibility of Copeptin improving the scenario of early diagnosis of acute MI [64, 65] and its possible role in prognostication. Early detection of AMI using cardiac biomarkers of myocardial necrosis remains much limited since these biomarkers do not rise early in the first hours from onset of AMI. But early identification of myocardial infarction in chest pain patients is crucial to identify patients at risk and to deliver a fast treatment initiation. Studies have been performed to determine whether Copeptin, an indirect marker for arginin-vasopressin, adds diagnostic information to cardiac troponin in early evaluation of patients with suspected myocardial infarction.

Early detection using combination of Copeptin with conventional Troponin T assay

Many studies have compared combination of Copeptin with conventional TnT and the performance of conventional TnT alone. Study by Keller et al included patients with suspected acute coronary syndrome and Copeptin, troponin T [TnT], myoglobin, and creatine kinase-myocardial band were determined at admission and after 3 and 6 h. Combined measurement of Copeptin and TnT on admission improved the c-statistic from 0.77 to 0.9 in patients presenting within 3 h after chest pain onset [CPO] [p < 0.001]. Those presenting within 3 hours of chest pain the combination of Copeptin with a conventional TnT provided a negative predictive value of 92.4%. They concluded that combined determination of troponin and Copeptin provides a remarkable negative predictive value virtually independent of CPO time and therefore aids in early and safe rule-out of myocardial infarction [66]. Similarly in another study 487 consecutive patients presenting to the emergency department with symptoms suggestive of AMI had their levels of Copeptin measured at presentation. Copeptin levels were significantly higher in AMI patients compared with those in patients having other diagnoses. The combination of troponin T and Copeptin at initial presentation resulted in an area under the Receiver-operating characteristic curve of 0.97, which was significantly higher than the 0.86 for troponin T alone [p < 0.001]. A Copeptin level <14 pmol/l in combination with a troponin T <0.01 Micro g/l correctly ruled out AMI with a sensitivity of 98.8% and a negative predictive value of 99.7% [67]. Thus the additional use of Copeptin seems to allow a rapid and reliable rule out of AMI already at presentation and may thereby obviate the need for prolonged monitoring and serial blood sampling in the majority of patients.

Early detection using combination of Copeptin with high sensitivity Troponin T assay

Copeptin has a distinct release pattern in patients with ST-elevation AMI, peaking within the first hour after symptom onset before conventional cardiac biomarkers and falling to normal ranges within the first day. Studies have been carried out comparing the release pattern of high sensitivity cardiac troponin [hs-cTnT], conventional cardiac troponin with Copeptin. Patients undergoing successful primary percutaneous coronary intervention [PCI] for a first ST-elevation AMI presenting within 12 h of symptom were included in the study where blood samples were taken on admission and at four time points within the first 24 h

after PCI. In contrast to all other markers, Copeptin levels were found to be already elevated on admission and were higher with a shorter time from symptom onset to reperfusion and lower systolic blood pressure. Copeptin levels peaked immediately after symptom onset and normalized within 10 h. In contrast, CK-MB, cTnT, and hs-cTnT peaked after 14 h from symptom onset and decreased more gradually. The study concluded that Copeptin is elevated in the early hours after the onset of an ST-elevation AMI when other conventional cardiac biomarkers are still low, further studies are required to determine the exact role of Copeptin in AMI suspects presenting within the first hours after symptom onset. [68].

Similar studies have been done to compare the performance of hs-cTnT along with Copeptin, and the performance of hs-cTnT alone, measured at admission and subsequently after 3 hour gap in patients of acute coronary syndrome of <6 hours' duration after onset of symptoms. Meune et al performed a study where fifty-eight consecutive patients of coronary syndrome were included. Measured on admission, hs-cTnT concentration was>14ng/mL [99th percentile] in 22 patients with acute coronary syndrome; repetition of the measurement at 3hours and 6hours identified three and four additional patients, respectively. The combination of Copeptin with hs-cTnT determined on admission identified 26 patients with acute coronary syndrome, with a negative predicted value of 82.6%. The area under the receiver operating characteristic curve was 0.90 for hs-cTnT measured on admission, and 0.94 if repeated at 3hours and 6hours or combined with Copeptin measurement at admission. Though the increase was found to be statistically non-significant this prospective study demonstrated that a dual marker strategy that combines hs-cTnT with Copeptin increased slightly the detection of acute coronary syndrome at admission [69].

Another trail prospectively tested whether Copeptin adds information to that provided by an hscTnT assay in the early evaluation of patients with suspected acute myocardial infarction, particularly non–ST-segment elevation myocardial infarction. Giannitsis et al enrolled 503 patients with suspected acute coronary syndrome and onset of chest pain occurring within the previous 12 h. Copeptin was measured on presentation, and hscTnT was measured serially at baseline and after 3 and 6 h. For ruling out AMI, an hscTnT concentration >14 ng/L [99th percentile] plus a Copeptin concentration >14 pmol/L yielded a diagnostic sensitivity of 97.7%, a diagnostic specificity of 55.9%. Receiver Operator Curve analysis of the continuous biomarker values on admission demonstrated no added value of using this marker combination for ruling out AMI when hscTnT was used as the standard for diagnosing. They concluded that a strategy using Copeptin with hscTnT at pre specified cutoffs improves the ruling out of AMI, compared with using hscTnT alone; thus, this strategy could help to obviate a prolonged stay in the emergency department [70].

Prognostication using combination of Copeptin with Troponin T

Elevated cTn may represent a surrogate parameter integrating prognostic information from associated diseases. An elevated cTn is associated with an adverse outcome [71]. The reasons for troponin elevations in the absence of myocardial ischemia are not fully understood

but may be associated with higher burden of atherosclerosis [72], more complex coronary lesions [73], depressed LV function, associated cardiac co morbidities, and severely impaired renal function [74]. Use of high sensitivity cTn assays has further improved risk stratification by detecting patients at risk who were previously not detected by conventional cTn assays including small MIs [75], patients in earlier stages of chronic pulmonary hypertension or acute and chronic heart failure [76,77]. In ACS several other biomarkers have been identified to provide independent and additive prognostic information to cTn. However little is known about the added value of these biomarkers when hsTn is used instead of conventional cTn. Recently in a study it was found that Copeptin not only improved rapid rule-out AMI but also helped to identify patients at higher risk for adverse outcomes [78].

Prognostication using combination of Copeptin with other markers

Not only is Copeptin a good prognostic marker for heart failure but also an emerging prognostic marker in patients suffering from AMI. AMI is associated with left ventricular dysfunction and clinical heart failure. Copeptin has been labeled as a significant independent predictor of death or heart failure in post MI settings and may provide prognostic information as pointed out by various studies. Comparison between the prognostic value of Copeptin and an established marker, N-terminal pro-B-type natriuretic peptide was done and it was found that Copeptin is elevated in patients who died or were readmitted with heart failure compared with survivors. Both markers were significant independent predictors of death or heart failure at 60 days. The study concluded that Copeptin may predict adverse outcome, especially in those with an elevated N-terminal pro-B-type natriuretic [>900 pmol/L]. Copeptin is thus a strong prognostic marker in patients with heart failure after an acute myocardial infarction [79].

Kelly et al [2008] performed a similar study in which subjects having AMI were assessed during the follow up. Copeptin was found to be associated with ventricular remodeling [80].

Comparison of the prognostic value of Copeptin, with B type natriuretic peptide [BNP], and N-terminal pro-BNP [NT-proBNP], on death or a composite cardiovascular endpoint in patients who developed heart failure after an AMI was done in another study. From a subset of 224 patients of the OPTIMAAL study, blood samples were drawn at a mean of 3 days after AMI. A doubling of Copeptin was related to a 1.83times increased risk of mortality [P < 0.0001]. Receiver operating characteristic curves indicated that Copeptin was a stronger predictor of mortality compared with both BNP and NT-proBNP[81].

One of a very recent study Biomarker Copeptin in patients with acute myocardial infarction has also endorsed similar views that Copeptin not only improves early diagnostic performance for AMI when used in combination with troponin for the initial blood draw in patients presenting to the emergency department with symptoms consistent with acute coronary syndromes but is prognostic for outcome.

CONCLUSION

An obstacle with hsTn assays is that the higher sensitivity results in a substantially higher rate of patients with analytically true positive troponin results not due to ACS, reflecting acute or chronic myocardial injury [82]. It may be challenging to discriminate between AMI and non-coronary cardiac or extracardiac reasons of elevated cTn. Use of additional biomarkers or a panel of biomarkers appears attractive for the better understanding of the pathophysiological process behind AMI, and for refined risk stratification. However, current guidelines preclude any other biomarker for routine use because the incremental value over highly sensitive troponin tests has not been evaluated yet [83]. One of the main contenders of this honor remains Copeptin, use of which will simplify,   and therefore complement the judgment of clinicians and/or validated clinical severity score. This warrants more studies as Copeptin can be possibly used in the panel of investigations in those at presenting with chest pain in ER.

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