UTILITY OF COPEPTIN IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Copeptin, a surrogate marker for vasopressin, is increased immediately following an acute myocardial infarction (AMI). In several studies, using a single multi-marker strategy, copeptin in combination with either conventional or high-sensitive troponin drawn at presentation of patients with AMI was able to rule out AMI with high negative predictive value (NPV). Copeptin is also reviewed as a prognostic marker for predicting mortality and morbidity in AMI and allows risk stratification of patients into low, moderate and high risk patients. This review looked at past researches conducted on copeptin as either a diagnostic marker for those presenting to emergency department with chest pain, or its prognostic value.

Keywords: acute myocardial infarction, copeptin, troponin, diagnostic, prognostic

1.0 Introduction

Acute myocardial infarction (AMI) remains an important cause of mortality and morbidity worldwide. Establishing an early diagnosis allows appropriate treatment in time, and prevents development of complications, which improves outcome of the patient. Currently, the commonly used diagnostic biomarkers for AMI are serum troponin (I or C) and CK-MB (Alpert et al, 2000; Thygesen et al, 2007). Although considered as gold standard for ruling in the diagnosis of AMI, troponin is limited by its delayed release into circulation (detected at 3-hours and peak at 12 hours after an infarction) (Macrae et al, 2006; Thygesen et al 2010). In the early course of myocardial injury, patients with chest pain will often have undetectable levels of troponin on initial evaluation. However, positive troponin results can be seen on subsequent samples when repeated few hours later (Macrae et al, 2006; Thygesen et al 2010).
Given the importance of rapid triage for patients with chest pain syndromes and the numerous benefits from early intervention has led to the interest of combining troponin with other biomarkers such as copeptin, myoglobin and heart-fatty acid binding protein for early diagnosis of myocardial injury. This review will specifically look at the utility of copeptin in AMI.

2.0 Copeptin

Copeptin comprises of 39 amino acids, is glycosylated, and consist of a leucine-rich core segment. It is derived from the C-terminal part of pro-AVP (CT-proAVP) and is secreted in equimolar ratio with arginine vasopressin (AVP) during processing of the precursor peptide (Morgenthaler et al, 2008). The AVP system plays a vital function in regulation of endogenous stress response. Release of AVP is regulated by hyperosmolality, hypovolaemia, hypotension and release of angiotensin II. The vasoconstriction action of AVP is mediated by V1 receptor on smooth muscle cells and its anti-diuretic effect via V2 receptor in distal kidney tubules (Goldsmith, 1987; Fukuzawa et al, 1999).

Copeptin is a sensitive surrogate marker for AVP release. However, compared to AVP, copeptin is a much more stable analyte and easily assayed on an automated platform by chemiluminescence method (Morgenthaler et al, 2006). As a result, copeptin has been looked into as a biomarker for diagnosis and monitoring of sepsis (Morgenthaler et al, 2007) and as prognostic indicator for pneumonia and lower respiratory tract infections (Müller et al, 2007; Stolz et al, 2007) as well as stroke (Lyold-Jones et al, 2009; Whiteley et al, 2009).

2.1 Current biomarker for diagnosis of myocardial infarction

Troponin (I or C) is a specific marker of myocardial necrosis and is recommended by current guidelines for detection of AMI (Thygesen et al, 2010). Their measurement by conventional assay has been used for many years worldwide. The introduction of highly sensitive troponin (hs-Tn) assay, which could detect concentration 10 folds lower than the conventional assay further improves the diagnostic accuracy and early detection of AMI (Reichlin et al, 2009; Keller et al, 2009). Despite hs-Tn ability to detect myocardial necrosis earlier than the conventional troponin assay, a troponin-blind interval still remains due to delayed release of troponin after a cardiac event (Eggers et al 2004). A second re-sampling for troponin is required for diagnosis; especially for those with non-ST segment elevation myocardial infarction (NSTEMI) resulting in overcrowding of emergency department (ED). Thus, inclusion of a biomarker which is released immediately in the event of an endogenous stress (independent of cell necrosis) may improve rapid diagnosis of AMI.

2.2 Copeptin as a biomarker for myocardial infarction

Copeptin levels were found to be highest on day 1 following an AMI, and subsequently decline to a stable plateau at days 2 to 5 which is still elevated compared to healthy controls (Khan et al, 2007). Several landmark publications showed that combining conventional troponin with copeptin significantly improved early diagnosis of AMI (Reichlin et al, 2009; Keller et al, 2010; Chenevier-Gobeaux et al, 2013). Copeptin increased to levels more than 14 pg/ml within 4 hours of symptom onset despite a negative cardiac troponin result. (Reichlin et
A copeptin cut off of < 14 pg/ml and a troponin T level of < 0.01 ug/L taken at the time of presentation rules out AMI accurately and rapidly (sensitivity and negative predictive value (NPV) of 98.8% and 99.7% respectively) (Reichlin et al, 2009). This was also confirmed in a larger population study (Keller et al, 2010). Sampling the two biomarkers at presentation improved the c-index for detection of AMI (0.94 compared to 0.85 when using troponin T alone). This finding is especially superior in those coming in within 3 hours of symptom onset. In contrast, combination of myoglobin and troponin T has a less ameliorative effect compared to when used in combination with copeptin. (Keller et al, 2010). The Copeptin Helps in the Early Detection of Patients with Acute Myocardial Infarction (CHOPIN) trial, involving 16 different centres and 1,967 consecutive patients presenting with chest pain showed that negative results for both copeptin and troponin I (TnI) ruled out AMI in 58% of patients without the need for a repeat blood sampling. Inclusion of copeptin to the initial TnI reduces the average time-to-decision for diagnosis of AMI from 2.96 to 1.80 hours, assuming a 3 hours interval to the second TnI sampling (Maisel et al, 2013).

Several recent studies had looked at the ability of copeptin in combination with troponin (either hs-Tn or conventional assay) to rule out NSTEMI and unstable angina for differential diagnosis of patients presenting with chest pain to ED (Giannitsis et al, 2011; Meune et al, 2011; Charpentier et al, 2013). Patients with confirmed diagnosis of STEMI were excluded from these studies, as the use of biomarkers in these patients were of a lesser value since the diagnosis could be made by ECG findings (Giannitsis et al, 2011; Charpentier et al, 2012; Thelin et al, 2013). Charpentier et al, 2013 looked at the performance of combining initial high sensitive troponin I (hsTnI) and copeptin for rapid rule out of NSTEMI in ED. The combination of these 2 biomarkers for NSTEMI diagnosis gave a sensitivity of 96.6% and a negative predictive value (NPV) of 99.1% when copeptin cut off value of < 12 pmol/L was used. Although there was an incremental value of adding copeptin in ruling out NSTEMI, the sensitivity using this single draw strategy was considered low for use in clinical practice (Charpentier 2013). Similarly, several other studies have obtained a similar NPV and sensitivity in NSTEMI patients (Meune et al, 2011 Thelin et al, 2013). For acute coronary syndrome (including NSTEMI and unstable angina) diagnosis, the combination of initial high sensitive troponin T (hsTnT) and copeptin had a significantly higher sensitivity than taking hsTnT alone with sensitivity of 83% and NPV of 91% (Thelin 2013). However, it was again insufficient to safely rule out acute coronary syndrome (ACS) in clinical practice. Eighteen out of 107 patients (3 NSTEMI and 15 unstable angina) would be misdiagnosed as non-ACS with this combination. Interestingly, the combination of these 2 biomarkers gave a significantly higher sensitivity for ACS diagnosis compared to a repeat hsTnT measured 3-4 hours later, thus enabling an earlier risk stratification for patients with chest pain (Thelin 2013).

Möckel et al, 2015 reported the research findings of a randomized controlled trial involving 902 patients with acute chest pain with initially negative troponin results, who were randomly assigned to either a standard care arm or to the experimental arm which underwent a copeptin assay. In the standard group, patients were managed according to the current guidelines for the management of patients with suspected ACS. In the copeptin group, further patient management was dependent on the copeptin result. At 30 days of follow-up, the rate of major adverse cardiovascular events (MACE) defined as all-cause death or survived sudden cardiac arrest, acute MI, rehospitalisation for ACS, acute unplanned percutaneous coronary intervention, coronary artery bypass graft, or documented life-threatening arrhythmias was similar in both groups. They concluded that single multi-marker strategy of troponin and...
copeptin in patients suspected of ACS allows for rapid rule out of AMI of low to intermediate risk patients is safe and reduces length of stay in ED.

2.2.1 Prognostic value of copeptin

In recent past, copeptin has been looked at as a valuable prognostic marker for patients with chronic (Neuhold et al, 2008; Gegenhuber et al, 2007) and acute destabilised heart failure (Voors et al, 2009). Khan et al, 2007 was the first to show the prognostic value of copeptin in AMI patients. They had included 980 patients with AMI (both STEMI and NSTEMI) and measured copeptin and NT-proBNP at days 3 to 5. Taken individually, both copeptin and NT-proBNP were powerful predictors of death or heart failure readmission at days 60. When combined together, they added further prognostic information, enabling patients to be stratified to either low, intermediate, or high-risk groups. Copeptin was particularly useful in patients with high NT-proBNP levels ($\geq$ 900 pmol/L). In these patients, copeptin level $\geq$ 7 pmol/L defines high-risk group and predictive of poor outcome. Hopefully, in future it will be used to guide appropriate therapy in high-risk patients. However, neither of these biomarkers was predictive of recurrent AMI.

In another study (subset of OPTIMAAL study), the prognostic values of copeptin, NT-proBNP, and BNP were compared in predicting mortality and composite cardiovascular endpoint (including death, AMI, stroke, and/or resuscitated cardiac arrest) in patients who developed heart failure in acute phase post AMI (Voors et al, 2009). Higher levels of copeptin, BNP, and NT-proBNP were all significantly related to both mortality and the composite cardiovascular endpoint. However, the predictive value of copeptin for mortality seemed stronger than the other two biomarkers. Furthermore, an increase in copeptin measurement a month after baseline was associated with increased risk of death and composite cardiovascular endpoint. Although serial copeptin measurements during follow-up may provide added-value, further evaluation of copeptin guided management requires evaluation in a larger population.

In the CHOPIN trial, based on the receiver operating characteristic (ROC) curve of time-dependent area under curve (AUC) for survival up to 180 days, it showed that copeptin AUC value was greater than TnI at day-30 suggesting copeptin as a strong short-term predictor of death. However, the AUC value for TnI was greater than copeptin at day-90 until day-180 suggesting TnI as a long-term predictor of death (Maisel et al, 2013). Both markers were independent of each other and combining them provided added significance.

3.0 Conclusion

Copeptin is a potential biomarker to be used clinically as a diagnostic as well as prognostic marker of acute myocardial infarction. For diagnosis, its use in combination with troponin aids in the decision-making for patients with chest pain, especially in those who presents early to the emergency department after the onset of symptoms. Future research is however required to determine the cost effectiveness of this multi-marker strategy.
References


