Mini Review

Potential Clinical Application of Novel Cardiac Biomarker (Troponin) and Stress Marker (Copeptin) for the Diagnosis of Acute Myocardial Infarction in the Emergency Department

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Abstract

Acute myocardial infarction is the major cause of death and disability worldwide, with an ongoing increase in incidence every year. Therefore, diagnosis of acute myocardial infarction should be made early and accurately to decrease the associated mortality and morbidity. The current gold standard cardiac biomarkers (Troponin and CKMB) for rapid rule in and rule out for acute myocardial infarction has downside since these biomarkers do not rise within first hours from onset of AMI. The delayed increase in detectable circulating levels of these markers contributes to delay in diagnosis and therapy in patients presenting early to the emergency department. The use of Copeptin (AVP), an anti-diuretic hormone of the hypothalamic pituitary axis which rises early after AMI has a good diagnostic accuracy when used together with cardiac troponin. This dual marker strategy of combining troponin and copeptin safely rule out acute myocardial infarction with high sensitivity and negative predictive value of >99%. These novel markers are not only used for establishing the diagnosis of AMI but also helpful for determining prognosis and further stratifying patients at high risks that would determine the therapeutic approach.

Keywords: Acute myocardial infarction; Copeptin; Tropinin; sST2

Introduction

Acute Myocardial Infarction (AMI) is defined as a clinical cardiac event resulting in death of myocardial tissue caused by ischemia [1]. Rapid assessment of these patients is critical to direct further diagnostic and therapeutic strategies. The diagnosis of acute myocardial infarction is based on symptoms, signs and findings on the electrocardiogram but in some patients these findings are nondiagnostic. In this patient population the use of cardiac biomarker which indicates cardiac tissue necrosis, of which troponin and Creatine Kinase Isoenzyme (CKMB) are prefered markers, play a pivotal role [2,3]. These novel markers allow for rule in of AMI within 3 hours after presentation in majority of patients [4] and offer the opportunity to initiate appropriate, evidence based treatment strategy [5,6].

The major drawback of current troponin assays is sensitivity deficit at presentation due to delayed release of circulating levels [7]. Therefore AMI exclusion requires prolonged period of monitoring for 6 to 9 hours and serial blood sampling, the grey zone for troponin elevation which consequently leads to overcrowding in the emergency department and increases the associated cost every year [8,9]. The vast majority of patients presenting to the emergency department with chest pain turn out not to have AMI [10]. One quarter to one third of patients with AMI present without significant ECG changes indicative of ischemia; therefore ECG is of little help to rule out AMI [10,11]. Currently, the process for AMI exclusion is time and cost consuming [11]. A fast and reliable method for differential diagnosis must be established.

In this setting, Arginine Vasopression (AVP), also known as antidiuretic hormone is one of the key hormone of hypothalamic pituitary-adrenal axis and osmostic control of homeostasis. Copeptin, a 39 peptide amino acid, is the C-terminal portion of the pro- AVP and is released together with AVP during the processing of precursor peptide [12]. However due to its unstable nature and rapid clearance from the plasma, measurement of AVP is rarely indicated [13-15]. Copeptin on the other hand is more stable and is easier to measure and is secreted in equimolar amounts with AVP [16]. In recent years, copeptin as marker of acute endogenous stress hormone has been demonstrated in different clinical conditions such as sepsis [15,17] pneumonia, lower respiratory tract infections [18,19], heart disease [20-22] and stroke [23,24]. The pathophysiology of copeptin secretion is therefore independent of cardiac cell necrosis and involves the body's response to acute stress/injury.

An increase in copeptin concentrations after acute myocardial infarction was first reported by khan et al, with highest values reported on day 1 and a subsequent decline over next 3 to 5 days [21]. Gu et al. have demonstrated that copeptin peaks within the first hour after symptom onset, falling to normal ranges within the first day [25]. Copeptin is an excellent surrogate of AVP which is shown to be elevated in AMI [26,27]. In sheep model of AMI, the peak response of AVP occurred at 40 minute after embolization and AVP was elevated for >12 hour [25]. The accuracy of copeptin in the detection of AMI has been highlighted in previous studies. In these studies, the accuracy of copeptin alone was limited, but it added incremental value to the conventional cardiac troponin assay, and was even more valuable early after onset of symptoms [21,28].

The focus of this review is to highlight the clinical importance of adding stress marker (copeptin) to conventional cardiac assays and their application in fast and accurate diagnosis of acute myocardial infarction in emergency settings.

The leicesture Acute Myocardial infarction peptide study proved the usefulness of combination of copeptin level <14 pmol/l and troponin level <0.01ug/l. to rule out AMI, with negative predictive value (NPV) of 99.7% and higher sensitivity (98.8%). This finding from LAMP study concluded copeptin as a potential cardiac marker in 2007 [21].

The additional incremental value of copeptin to troponin was first elucidated by Reichilin et al., in management of 487 consecutive patients with chest pain presenting to the ED. In those patients with diagnosis of AMI (17%), copeptin concentrations were already elevated 4 hour after onset of symptoms when the concentration of troponin was undetectable in many patients. As copeptin concentrations declined, and troponin concentrations increased, the gap was bridged which resulted in an additive value of both markers for the diagnosis of AMI. The Area under the curve (AUC) of troponin alone at presentation when compared to combination of copeptin and troponin was increased from 0.86 to 0.97. A copeptin level (<14 pmol/l) in combination with negative troponin (<0.01 ug/l) correctly ruled out AMI with a high sensitivity (98.8%) and a negative predictive value of 99.7% [7].
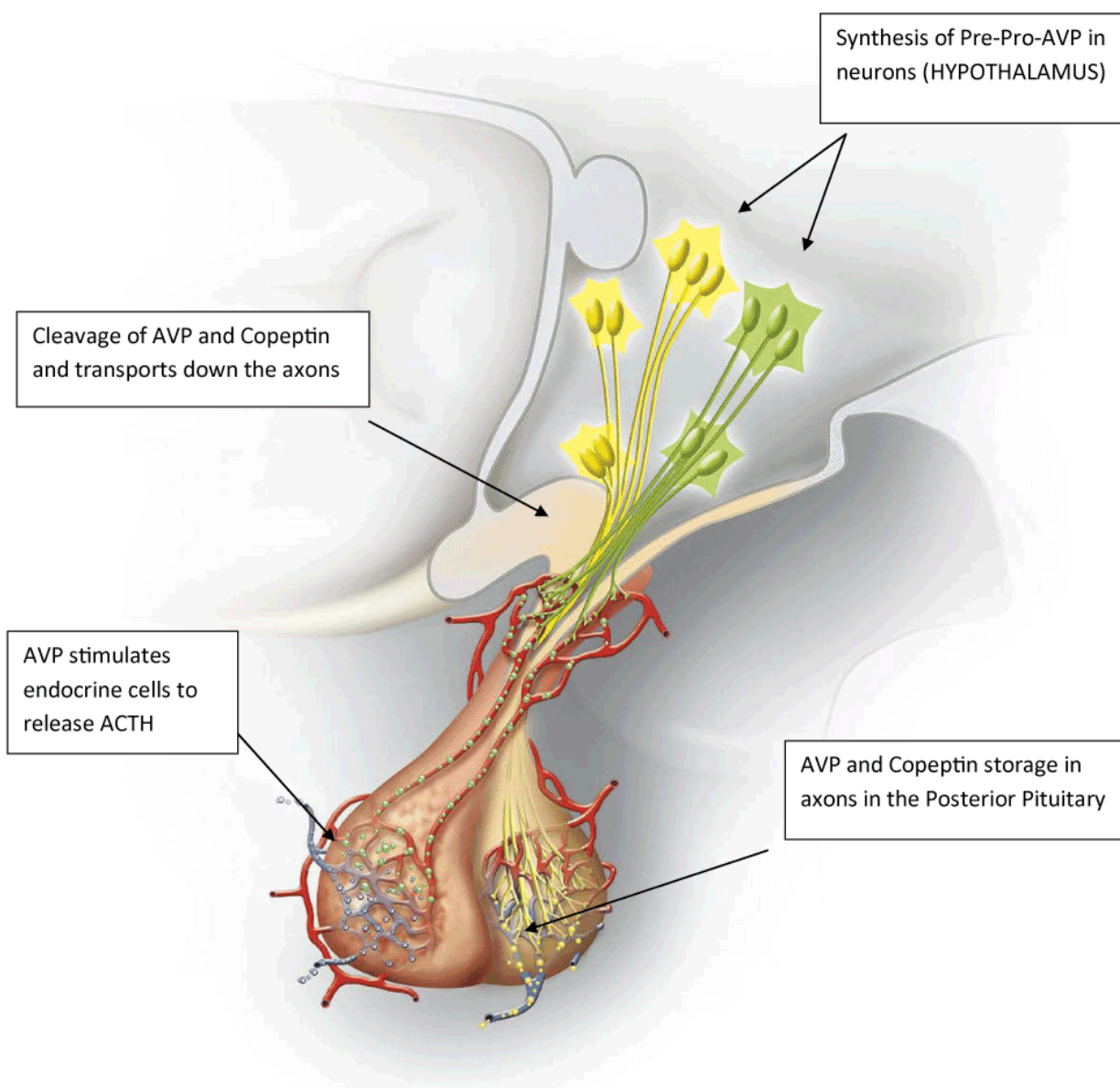
Figure 1: The release of Vasopressin (AVP) and copeptin (CP) from the hypothalamus and pituitary ACTH, adrenocorticotropic hormone (Adopted from Nickel et al. BMC Medicine 2012, 10:7)

A second study by keller et al. confirmed these findings and demonstrated that the combined measurement of copeptin and troponin T improved the c-statistics from 0.84 for TnT alone to 0.93 for a combination of copeptin and troponin T. This finding was more significant in patients presenting within 3 hour after symptoms onset. In this group the combination c-statistics increased from 0.77 to 0.9 with a negative predictive value of 92.4% [28].

Similarly, CHOPIN is the largest multi-center trial of this type to date with 1,967 patients with chest pain presenting to an emergency department within 6 hour after chest pain onset. In these patients AMI was the final diagnosis in 7.9%. This large, multicenter trial confirms that the combination of a negative troponin and negative copeptin on presentation allows the rule out of AMI for 58% patients with >99.2% negative predictive value. In addition copeptin value (>14 pmol/l) was able to detect greater numbers of patient with Acute myocardial infarction and Non ST elevation myocardial infarction at presentation when cardiac troponin was undetectable. Both elevated copeptin and troponin were predictors of death at 180 days and were independent of age and each other with additive negative predictive value [29].

These results are true for patients presenting early after onset of symptom and it is likely that the added benefit of copeptin may loss significance when present late. To date, conventional cardiac biomarkers have limited ability in ruling out AMI in patients presenting with early symptoms suggestive for an AMI but with nondiagnostic findings on ECG [30]. The current findings from the CHOPIN together with previous study by Reichlin et al suggest that copeptin may be potentially valuable marker on top of cardiac troponin for early detection of AMI. Based on these studies, repeated ECG monitoring and serial blood sampling for biomarkers , could be limited to only those patients positive for either troponin(>0.01ug/l)/ or copeptin (>14pmol/l) while those patients whose both markers are negative, no longer required repeated ECG monitoring and serial blood sampling for biomarkers. This dual marker strategy which combines troponin and copeptin can be used for rapid and reliable means for exclusion of AMI. This approach would save patients from expensive monitoring for markers and laboratory assays [7]. Recent studies have also indicated that soluble serum ST2 member of the IL-1 receptor family is significantly elevated during the process of acute myocardial infarction. It is reported that soluble ST2 levels are increased in the serum of patients 1 day after myocardial infarction. Furthermore, ST2 serum levels predict outcome in post AMI patients and has an independent predictive value for the prognosis of AMI patients [31-36]. These data suggests that measurement of serum levels of ST2 may provide insight into the hemodynamic burden of the myocardium. So measurement of copeptin and sST2 in blood samples could be a clinical prognostic biomarker useful in risk stratifications of patients suffering from acute myocardial infarction. Additional studies are necessary to evaluate the prognostic value of ST2 in conjunction with copeptin and other available biomarkers. Thus, these novel biomarkers needs to be further evaluated in larger prospective and interventional studies to produce better evidence for a routine clinical evaluation of patients suffering from acute myocardial infarction and other cardiovascular diseases.

Conclusion

In the Emergency department patients presenting with acute chest pain suggestive of acute myocardial infarction (AMI), the combination of cardiac troponin and copeptin, provide faster exclusion of AMI, yet with very good accuracy. In addition to save money and time ,rapid

exclusion of AMI would lead to better management of high risks patients that would hopefully reduce the adverse events related to AMI such as heart failure and death. Early detection of AMI would reduce the mortality and morbidity. These novel markers are not solely used for diagnosing AMI but also used in stratifying risks and prognosis that would determine the therapeutic approach of these patients.

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