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Copeptin: A Neuroendocrine Biomarker in Acute Myocardial Infarction

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Authors' contributions

This work was carried out in collaboration between all authors. All authors were involved in data and information gathering, analysis, organization, manuscript writing and critical reviewing. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Copeptin is a novel neuroendocrine peptide recently introduced to the field of acute medicine biomarkers. It is 39 amino acids glycopeptide cosynthesized with arginine vasopressin (AVP) and released together in stoichiometric pattern from the hypothalamus upon stimulation of AVP release. Due to difficulties of AVP assay, copeptin largely replaced it in clinical assay as surrogate biomarker because copeptin has easier and more valid measurement methods. In acute stress condition, copeptin rises and reflects stress level exactly like AVP which was largely known as mediator of non-specific stress conditions beside its prominent role in water homeostasis. Acute myocardial infarction (AMI) is an acute stress state in which plasma copeptin rises. Early identification of AMI is a problem due to the delayed appearance of the cardiospecific troponins which start to rise within 6-9 hours from the onset of chest pain. In the recent years many studies concluded that, when copeptin is combined with cardiac troponins in diagnosis of patients presenting with acute chest pain in early hours, it accelerates early rule in of AMI and rule out of non-MI patients. This review article discusses the biochemical and physiological basics of copeptin beside its clinical diagnostic value in AMI according to results and conclusions of some studies carried out on copeptin in AMI diagnostic field.

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1. INTRODUCTION

Copeptin, also named as the c-terminal glycoprotein of provasopressin [1,2] and AVP associated glycopeptide [3]. It was first time defined by Holwerda in 1972 [4]. It is considered as a novel neuroendocrine hormone of the vasopressinergic system [3].

2. COPEPTIN BASIC BIOCHEMISTRY (STRUCTURE AND SYNTHESIS)

Copeptin is a glycosylated 39 amino acid long peptide with leucine rich core segment [5]. Its molecular weight is 5000 daltons that was documented by the aid of gel exclusion chromatography [6,7]. This molecular weight doesn't conflict with the theoretical anticipation of deglycosylated copeptin which was 4021 daltons. Its glycosylation was proven by the lectin chromatography [8,9].

Copeptin is synthesized from the same ancestor gene of the AVP which is located on the 20^{th} chromosome p13 in tandem arrangement and reverse order with oxytocin gene. After its transcription, the copeptin will be derived from the third exon of the three exons encoding mRNA together with the last 17 amino acids of the C-terminus of neurophysin-II (NP-II). The other two exons will be translated into the signal peptide, AVP and the rest of NP-II (Fig. 1) [10]. Upon translation of preprovasopressin mRNA, 168 amino acids long preprovasopressin will be produced. This 168 amino acids peptide will be segmented into 23 amino acid signal peptide, 9 amino acid AVP, 93 amino acid disulfide rich or cysteine rich NP-II and 39 amino acid glycoprotein; copeptin [1,10,11].

The process of preprovasopressin segmentation is a result of a cascade of four hydrolytic enzymatic reactions mediated by *endopeptidase, exopeptidase, monooxygenase and lyase* respectively during its axonal transport from the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus to the neurohypophysis (Fig. 2) [1,12].

After removal of preprovasopressin signal peptide (23 amino acids), the provasopressin folds, and locating AVP inside NP-II binding pocket to protect AVP from proteolysis and to facilitate its packaging into the neurosecretory granules [12]. The pre-AVP is inserted into the endoplasmic reticulum and eight disulfide bridges are formed, seven in the NP-II and one in the AVP and the c-terminal glycoprotein of provasopressin is glycosylated and then packaged in the neuroendocrine vesicles to be transported from the SON and PVN into the posterior pituitary. The reaction completes at the level of neurohypophysis [1,12,13].

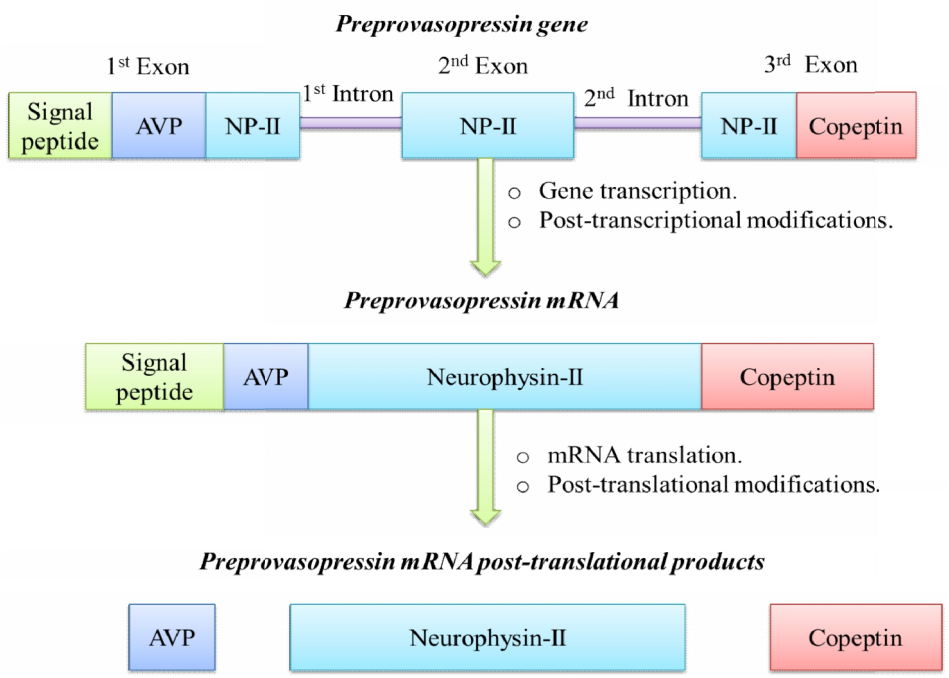

Fig. 1. Demonstration for AVP gene components and their products

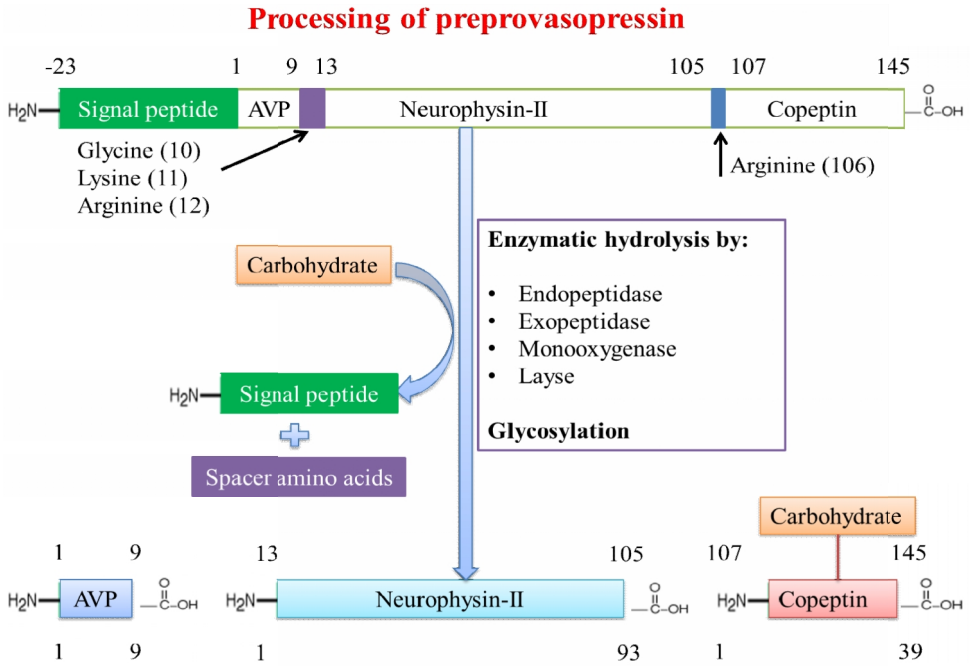

Fig. 2. Processing of preprovasopressin

3. MECHANISMS OF AVP/COPEPTIN RELEASE

Two mechanisms are involved in AVP precursor central synthesis and transport [5,11]. In the first mechanism, the magnocellular neurons of the SON together with the PVN provide the hypothalamic neurons whose axons traverse the base part of the hypothalamic median eminence to enter the posterior lobe of the pituitary gland. This is called the hypothalamic neurohypophyseal system or nerve tract [5,10]. During axonal transport, AVP, NP-II and copeptin are processed from their precursor preproprotein via four sequential enzymatic cascades [11]. Consequently, they are transported along the neurohypophyseal tract in neurosecretory vesicles to be stored in varicosities at the nerve terminal in the neurohypophysis (Fig. 3A) [14].

Another vasopressinergic mechanism which influence the pituitary gland starts in a normal, smaller neurons called; parvocellular neurons originating in the hypothalamic PVN and terminating in the median eminence region at the hypothalamus base [10]. This area is where hypothalamic releasing hormones, such as corticotropin releasing hormone (CRH) are also produced [5]. AVP and CRH synthesized within those parvocellular neurons are released into the long portal vein to affect the adenohypophysis (Fig. 3B) [14].Copeptin is usually co-secreted with AVP in an equimolar fashion upon stimulation of AVP release [3].

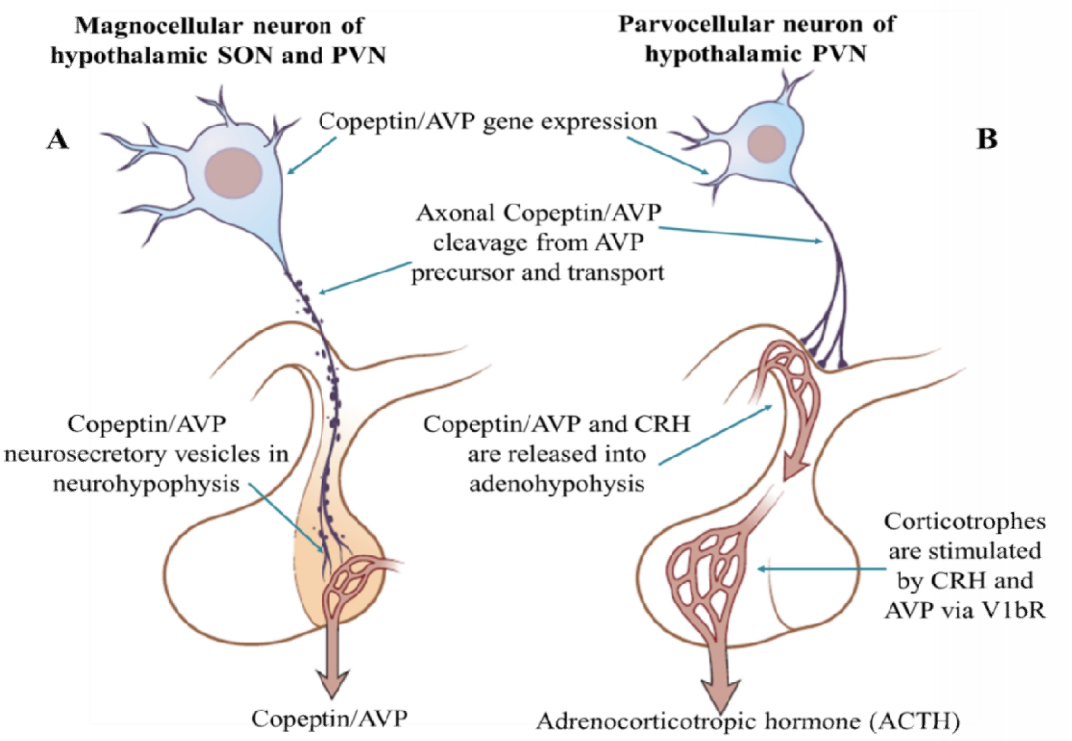

Fig. 3. The two central pathways for AVP/Copeptin synthesis and transport

4. PHYSIOLOGICAL FUNCTIONS OF AVP/COPEPTIN

AVP is a cyclic nonapeptide with intra-molecular disulfide bond between Cys4 and Cys9. It is also named as antidiuretic hormone due to its regulatory effects on blood volume. It produces its cellular effects through interaction with its three G-protein coupled receptors; the vascular predominant AV1a receptors (AV1aR), neuroendocrine AV1bR, also named AV3R, and renal AV2R [1,15].

The AV1aR are the most widely distributed and predominant receptors for AVP. Their physiological effects are mediated through activation of their coupled G_q protein and downstream cascade of phospholipase C/inositol triphosphate/protein kinase C system to increase intracellular calcium [16]. They are located in the endothelial smooth muscles, adrenal gland, myometrium, urinary bladder, adipocytes, hepatocytes, platelets, renal medullary cells, collecting ducts, spleen, testis and many CNS structures [1,10].Through these AV1a receptors, AVP can induce arteriolar vasoconstriction [5], cardiac inotropism [10], platelets aggregation, adrenal steroidogenesis, hepatic glycogenolysis, proliferation of cardiomyocytes, hepatocytes and smooth muscle cells [15], uterine contraction, gastrointestinal peristalsis, central regulation of arterial blood pressure, heart rate, body temperature, emotional learning, social memory and stress adaptation [1,17].

The AV1b receptors are termed AV3 receptors, coupled to Gq protein that activates the same intracellular cascade as AV1R. They are located predominantly in the CNS on the corticotrophic cells in the adenohypophysis [18]. They have important neuroendocrine control mechanisms for release of ACTH from the anterior pituitary through activation of corticotropin releasing hormone [5,18,19]. These AV3-receptors are considered as active neuroendocrine receptors, because their activation also seems to promote the secretion of other hormones including prolactin, growth hormone, insulin, angiotensin, endothelin, and atrial natriuretic peptide, although the in vivo relevance of these properties remains to be established [3,20]. Finally, V3 receptors have possible roles in social behavior and regulation of mood [19,21].

The distal convoluted tubules (DCT) and collecting duct (CD) cells represent the major sites of AV2R distribution [17,18]. Those receptors are G_s coupled receptors activate adenylyl cyclase/˺5 cyclic adenosine monophosophate/protein kinase A system that mediates AVP conservative effect on water [19]. AV2 receptors stimulate aquaporin protein gene expression and aquaporins integration in the cell membrane of DCT and CD to enhance water permeability at the luminal side of CD, then water will be translocated to the basolateral surface, to the systemic circulation [17,1]. The vascular endothelial cells contain AV2R that have important role in blood coagulation mechanisms, because they increase plasma level of von Willebrand factor, clotting factor VIII (antihemophilic factor) and plasminogen activator [1,22,23].

Copeptin's physiological function is not well-established, but many hypotheses for its functions are available. One of them suggested copeptin as prolactin releasing factor [24], but this was disproved later [25]. Another hypothesis suggested also, copeptin together with NP-II serve as AVP carriers during axonal transport from the hypothalamic SON and PVN into the neurohypophysis [26]. Later on, it was hypothesized that, copeptin is essential in proteolytic maturation, proper folding and structural stability of provasopressin [1,3,27]. The mechanism of this was suggested to be through copeptin interaction with the calnexin-calreticulin system [12]. Calnexin and calreticulin are two proteins of 90 and 60 KD respectively. Calnexin-clareticulun system is a member of the endoplasmic reticulum

chaperones, responsible for monitoring of glycoproteins folding to enhance properly folded active proteins production [28]. This hypothesis was found to be involved in the pathogenesis of central diabetes insipidus in which the absence of copeptin resulted in pro-AVP misfolding. Also, it explained why oxytocin stable precursor lacks copeptin [12].

5. COPEPTIN CLINICAL BIOCHEMISTRY

Copeptin release is mediated by the same biological mediators for AVP release as both are regulated solely at the transcriptional level [1]. Plasma copeptin is tightly related to plasma AVP in response to physiological and pathological stimuli [9,28].

Normal plasma level of copeptin in healthy volunteers ranges between 1.0-12 pmol/L with median value below 5.0 pmol/L. Its level in men is slightly higher than women with difference in median value by 1.0 pmol/L [5,12]. Copeptin plasma level changes in response to alteration in plasma osmolality similar to AVP [25]. Plasma copeptin is low in patients with central diabetes insipidus [29] and high in patients with hypovolemic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion [30]. Severe disease such as; stroke, severe illness as in systemic inflammatory response syndrome, shock, stress conditions and cardiovascular diseases exhibit pronounced release of AVP and increase in plasma copeptin level [3,5,31]. This obvious in vivo tight correlation between copeptin and AVP promotes copeptin as an ideal surrogate biomarker for the vasopressinergic system [3,32].

6. COPEPTIN/AVP AS NEUROENDOCRINE PEPTIDES OF STRESS

When the physiological homeostatic balance is disturbed upon exposure to strenuous internal or external stimuli, stress develops. This abnormal homeostatic imbalance will be compensated by development of stress adaptation response through effective interaction of a network of adaptive mediators that may help in re-establishing the normal physiological status [32,33]. This effective interaction for survival and adaptation for life threatening stress condition is achieved via coordination and integration of brain sensory signals, autonomic nervous system and endocrine system [16].

Activation of the hypothalamic-pituitary-adrenal (HPA) axis represents the major neuroendocrine adaptive response for stress conditions [16,32]. This axis becomes activated when the stressor gives an input to the brain stem and limbic system where emotional responses are controlled [33,34]. Then the parvocellular neurons of the hypothalamic PVN will be stimulated to synthesize and release both AVP and CRH into the portal circulation to affect the corticotrophic cells of the anterior pituitary, to stimulate ACTH synthesis and release which consequently stimulates adrenal cortisol synthesis and release [16]. In this mechanism, approximately 50% of parvocellular CRH neurons express AVP gene to be synthesized and released in synchronism with CRH into the anterior pituitary to operate its neuroendocrine V3R in the anterior pituitary to synergize CRH effect on ACTH production [5,16,20]. In addition to regulating HPA axis, AVP together with CRH have a central role in control of autonomic nervous system response to stress conditions [16]. The hypothalamic neuropeptide AVP regulates limbic system response to stress where it enhances behavioral stress response [35].

In 2008, Katan and his colleagues reported significant positive correlation between plasma copeptin and individual stress level with much more stability of samples relative to cortisol

that has physiological diurnal variation in plasma level, in addition to plasma cortisol assay challenges [36]. The vasopressinergic/CRH system has a significant role in conditioning to chronic stress as in obesity and diabetes. Recently, it is observed that, plasma copeptin level positively correlates to states of insulin resistance, diabetes mellitus, obesity, metabolic syndrome and diabetic nephropathy [37-39]. During acute illness, acute stress usually develops with high magnitude of plasma copeptin as neuropeptide of the AVP/CRH system [33]. These findings promoted copeptin introduction as diagnostic and prognostic biomarker in acute medicine [40].

7. COPEPTIN VERSUS AVP IN CLINICAL ANALYSIS

Many obstacles are challenging reliable AVP clinical assay. AVP has a short plasma half-life (5-15 minutes) beside its high in vivo affinity for platelets binding > 90%. AVP is highly unstable in vitro even at temperature of -20ºC due to its rapid biodegradation [3,7,12,27]. In addition to the time wasting analytical procedures (12-24 hours), careful samples handling, need for sample extraction and addition of protease inhibitors and cumbersome measurement should precede its assay [8,9,32]. Furthermore, AVP is a short nona peptide of small size which precludes more accurate sandwich enzyme linked immunoassay. This factor forced the use of less sensitive competitive immunoassay [9,12].

Due to the discussed pitfalls of AVP assay, the concept of using another equimolar physiologically nonfunctioning stable, stoichiometrically co-released peptide such as; copeptin from the same ancestor preprovasopressin was developed [12]. This concept in clinical practice wasn't new, because it had been used before with C-peptide as indirect indicator for plasma insulin level as both are derived from the same preproprecursor; preproinsulin [2,12]. Copeptin seems to be an ideal shadow for AVP in clinical assessment due to multiple advantages over AVP in clinical assessment. It is a highly stable molecule in vivo and in vitro. It can withstand in plasma and serum at room temperature for 7-10 days and 14 days at 4.0 ºC [8,12,28]. Copeptin assay techniques needs no special handling precautions for samples, samples extraction and preparation and could be done on both plasma and serum using minute volume of samples (50 µL) versus 1.0 mL for AVP. Copeptin assay is faster and the results are available within 1.0-5.5 hours according to the analytical method [7,12].

8. WHY COPEPTIN WAS SELECTED AS A SURROGATE BIOMARKER FOR THE VASOPRESSINERGIC SYSTEM OVER AVP PRECURSOR AND NP-II?

Despite of the large size of the prepro-AVP (168 amino acid peptide) and the different theoretical potential targets for antibodies binding, it wasn't possible to develop reliable assay procedure due to the presence of extremely short connecting peptides between its components (Gly-Lys-Arg between AVP and NP-II, and Arg only between NP-II and copeptin) [1,8,12].

For NP-II, it didn't seem as ideal representative for AVP, due to its complex structure of seven intermolecular disulfide bridges and its affinity to bind AVP [12]. Fig. 4 describes the advantages of copeptin over AVP in clinical assessment.

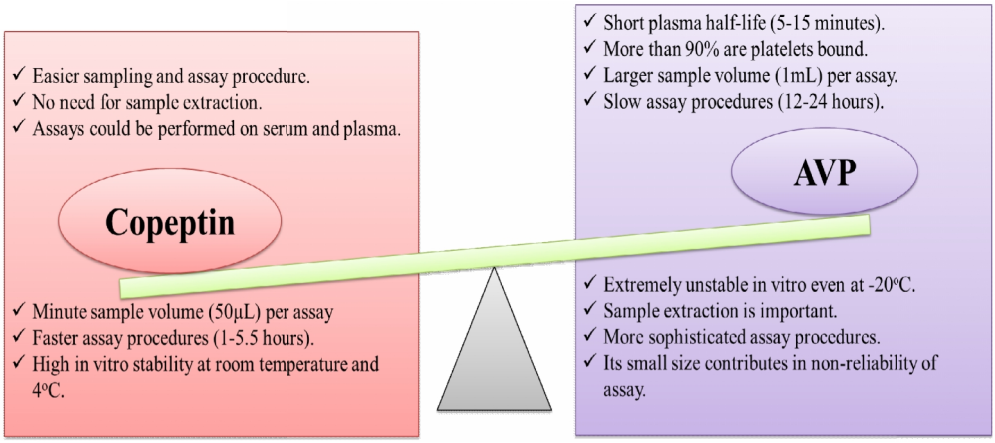

Fig. 4. Copeptin and AVP in clinical assay

9. DIAGNOSTIC ROLE OF COPEPTIN IN EARLY IDENTIFICATION OF AMI

Early detection of AMI, especially cases of ST-elevated myocardial infarction (STEMI) is crucial to accelerate the invasive and aggressive pharmacological reperfusion therapy that may improve the outcome and reduce morbidities and mortalities [41,42]. The recommendation of the American Heart Association/American College of Cardiology for management of acute STEMI patients is the immediate start of reperfusion therapy using percutaneous coronary intervention (PCI) and fibrinolytic drugs in order to re-perfuse the ischemic regions [43]. For patients identified early with Non ST-elevated myocardial infarction (NSTEMI), immediate catheterization for revascularization of the unstable coronary lesions may prevent development of ischemic complications that would develop during therapeutic intervention. Intensive antiplatelets therapy before PCI may reduce unstable lesions thrombotic burden and augments safety and successfulness of PCI [44].

According to the latest third international definition of myocardial infarction, the electrocardiographic abnormalities together with changes of cardiac troponins (cTns) level represent the key diagnostic elements for diagnosis of myocardial infarction in the emergency department [45]. cTns are without doubt golden standards in diagnosis of AMI and their plasma detection indicates myocardial necrosis with high specificity and good sensitivity in prospect to onset of symptoms [45,46]. cTns, is raised within 6-9 hours from the onset of symptoms giving sensitivity of 39-43% when the patient is admitted to the emergency department (ED) in the early three hours of onset [47,48]. Aside the delayed time between the onset of symptoms and appearance of cTns in the blood indicates myocardial damage regardless the underlying causes and multiple non-ischemic conditions may challenge the interpretation of causes of elevation in plasma cTns [46,49]. Thus, addition of another biomarker such as, copeptin may be more informative in reflecting myocardial ischemia, plaque rupture or other signals of early AMI and to be associated with a specific pathophysiological mechanism in AMI development [46].

A prospective cohort study was done by Reichlin et al. [50] on 487 consecutive patients admitted to ED with AMI suggestive symptoms with onset within 12 hours before admission, plasma cardiac troponin-T (cTnT), myocardial band of creatine kinase, myoglobin and copeptin had been measured at the time of presentation, 3, 6 and 9 hours later. Plasma

copeptin was higher than that of cTnT at the time of admission for patients with AMI who are presented in early 4 hours from the onset of symptoms with median value of 20.8 pmol/L, while cTnT level was below the detection limit of 0.04 µg/L in 35% of patients at presentation time. But copeptin added no value for patients admitted later who have positive troponin values. The diagnostic sensitivity for copeptin, cTnT, and combined biomarkers at early 4 hours of chest pain onset (CPO) was quantified by the receiver operator characteristic (ROC) curve which revealed area under curve (AUC) of 0.75, 0.86 and 0.97 respectively. In contrast, the combination of cTnT with both myocardial band of creatine kinase and myoglobin did not result in a significantly higher diagnostic accuracy as compared with cTnT alone. Correct early ruling out of AMI at presentation time was achieved by combining results of copeptin assay of ≤14.0 pmol/L and cTnT assay of ≤ 0.01 µg/L with 98.8% sensitivity, 77.1% specificity, 99.7% negative predictive value (NPV) and 46.2% positive predictive value (PPV). Hence, the added value of copeptin to cTnT assay accelerated clinical decision for rejection of non AMI patients without need for serial blood sampling for repeated cTnT measurement and prolonged monitoring time [50].

In another prospective study carried out on 1386 patients presented to ED with acute chest pain. Plasma copeptin, cTnT and other cardiac biomarkers were analyzed at the time of admission, 3 and 6 hours later. Keller and his colleagues [47] found that, plasma median cTnT level showed proportional increase with the time onset of symptoms, in contrast to that of copeptin which declined as the time go far from the onset. Copeptin median plasma level was 5 folds higher in AMI patients who admitted as early as 3 hours from CPO to 29.6 pmol/L in comparison to that of patients of non-cardiac chest pain (5.7 pmol/L) and those of unstable angina (5.45 pmol/L). Median cTnT in patients admitted within 3 hours from the onset was only 10% of the cut value of 0.03 ng/L. In patients presenting within < 3 h after CPO, the combination of copeptin and cTnT indicates highest diagnostic strength with AUC of 0.9 compared with addition of myoglobin to TnT. Combination of copeptin and TnT stayed superior with AUCs of 0.91, 0.92, and 0.93 in patients with CPO of <6 h and <12 h, and the overall population, respectively. They concluded that, copeptin and cTnT combination was superior to other single or combined biomarkers in identification of AMI in early hours of CPO [47].

A prospective multi-centric study was carried out by Ray et al. [51] on 430 patients with previous history of coronary heart disease admitted to the ED with CPO of 6 hours or less, with negative electrocardiographic findings and negative cardiac troponin-I (cTnI) diagnostic values at admission. Copeptin was measured blindly at presentation time, while serial sampling of cTnI at admission time, 3, 6 and 9 hours later was done. It was found that, the median serum copeptin level in patients with AMI is significantly different from the non-ischemic patients. No difference among STEMI and NSTEMI patients serum copeptin level. The area under the ROC curve for copeptin alone was significantly higher than that for cTnI alone. The combination of copeptin with cTnI showed an increased AUC in comparison with cTnI alone but not in comparison with copeptin alone.They defined the optimal copeptin threshold value as 10.7 pmol/L due to its association with a very high NPV, in association with the highest sensitivity, specificity and accuracy. This study concluded that, the combined assay for copeptin and cTnI for patients suffering from acute chest pain and suspected for NSTEMI with CPO less than 6 hours, provides NPV of 98% which enables clinicians to rapidly rule out AMI at presentation time [51].

Chenevier-Gobeaux et al. [52] investigated the sensitivity of combined cTnI and copeptin assay superiority over the conventional cTnI assay sensitivity in early diagnosis of AMI in a prospective multi-centric study carried out over 18 months on 317 out hospital patients over

18 years old admitted to ED with CPO less than 6 hours. Beside the routine clinical investigation measures, plasma cTnI and copeptin were evaluated serially at the time of admission, 3 hours to 9 hours. The median level of plasma copeptin in AMI group was significantly higher than other diagnostic groups (23.2 pmol/L vs 9.9 pmol/L, *P*=0.01). Regarding AMI diagnosis, the AUC of cTnI ROC curve was 93%, P<0.001 in comparison to 73%, P=0.002 for copeptin. Copeptin ROC curve revealed the optimum AMI diagnostic threshold > 10.7 pmol/L with 81% sensitivity and 53% specificity giving PPV of 21% and NPV of 95% with accuracy of 57%. Combination of patients having positive cTnI and/or positive copeptin significantly increased the sensitivity and the NPV in comparison to cTnI alone to be 98%. The final conclusion of this study stated that, the use of copeptin with cTnI may allow rapid and reliable rule out of the diagnosis of AMI [52].

Four hundred and seventy one patients admitted to ED suffering from acute chest pain with CPO less than 8 hours before presentation, over 6 months were investigated by Folli and his coleagues [53] for acute coronary syndrome (ACS) using double marker technique, which were the cTnT and copeptin in a multicenteric observational prospective study. This study aimed to examine if the combined copeptin and cTnT can correctly rule out the ACS and other non-cardiac chest pain. Plasma copeptin and cTnT values were detected at presentation time. As what was noticed in previous studies, they found plasma copeptin levels were much higher in patients with STEMI and NSTEMI much higher than those of unstable angina and other diagnosis group. Analysis of ROC curve data cleared a wider AUC for both copeptin and cTnT in STEMI (0.86 and 0.72) and NSTEMI (0.73 and 0.76). When combined together, the AUC became 0.89 and 0.86 in STEMI and NSTEMI respectively. Combination assay of copeptin and cTnT attained NPV of 86.6, 85.0 and 97.9 for those of ACS (STEMI and NSTEMI), whole population and those patients with life-threatening diseases other than ACS respectively. This study concluded the importance of copeptin in early rule out of patients with AMI and as an alarm signal for life threatening diseases [53].

10. WHAT CAUSES ELEVATION OF PLASMA AVP/COPEPTIN IN AMI?

It was noticed that plasma AVP significantly rises after AMI in both human and animals. However, the underlying causes of elevation were not clearly defined. Many hypotheses were developed to elucidate the mechanism of AVP/copeptin rise in AMI. One of them is the hypothesis of stress, suggests that, AVP/copeptin rise is a part of the rapid stress response against the stressful life threatening condition of AMI. In this response, AVP acts synergistically with both ACTH and cortisol as moderators of acute stress [2,5,47]. This hypothesis of stress was favored by many endocrinologists [3,5,54]. The hemodynamic hypothesis arose from studies on STEMI patients [47,54]. Acute changes in cardiac dynamics, cardiac under filling, and stimulation of cardiac baroreceptors as a response for reduced systemic blood pressure or direct tissue damage resulting from prolonged ischemia represent a striking trigger for stimulation of AVP/copeptin release [2,5,47,54,55].

11. IS COPEPTIN MEASUREMENT FOR CHEST PAIN PATIENTS TIME SAVING AND COST EFFECTIVE OR NOT?

A cost effective diagnostic measures and medical services should be in the primary priorities of health care facilities. To meet this goal, many local and international guidelines have been released which offer rapid and accurate diagnosis and reduce the tendency for overcrowding inside hospitals or ED [54].

AMI differential diagnosis from other causes of chest pain has a global interest from clinical and economical views [54]. The poor sensitivity of traditional methods for cTns measurement is the main cause of serial sampling and prolonged monitoring of patients for 12 hours to insure or exclude AMI, which is an expensive evaluation process [26,45,56]. Thus, novel biomarkers of different release pattern were introduced to accelerate the process of diagnosis and reduce costs of medical care. Copeptin is a general marker of stress and non-specific for the heart. Therefore, it is better to be combined with more cardio-specific biomarkers as cTns to enhance the specificity and sensitivity of both at early hours from CPO [47,50].

Copeptin exhibits a rapid increase in its plasma level immediately after the onset of chest pain [47,50-53], then declines after 4-6 hours due to its invivo degradation [9,54]. So, its value is highly obvious within the early 4 hours from CPO, particularly for NSTEMI patients with negative cTns at admission time [26,47,50,54].

Several studies concluded that, the combination of both copeptin and cTns provided fast ruling out of non AMI patients in cost effective manner for patients admitted within 4 hours from CPO [47,50,54,56-59]. One of them showed that, the combined copeptin/cTns assay can offer 30% reduction in the total cost of treatment in the ED as well as 74% reduction in the diagnostic and monitoring time in comparison to traditional cTns assay alone [58].

In contrast to the previous studies, a multi-center study intended to evaluate the diagnostic efficiency of multi cardiac biomarkers in acute chest pain patients concluded that, copeptin measurement is time wasting and cost ineffective [60].

This conclusion is not entirely true due to many reasons. First, this study included patients with chest pain within 12 hours from CPO. Timing of sampling is critical for achieving an accurate rule out of AMI with copeptin. The diagnostic significance of copeptin appears only for early admitted patients, where it showed NPV of 97.7-99% at cutoff value of 14 pmol/L when combined with cTns [47,50]. Patients admitted after the early 4 hours may have positive cTns in the first sample. Hence, copeptin measurement appears cost ineffective and time wasting.

Second, this study stated that, copeptin was more useful for patients presented earlier. Third, there was a criticism in this study, which is the minority of patients having AMI. Copeptin is a rule out biomarker for AMI, not for ACS where its plasma level in UA is much lower than in AMI [26,47,50,54,56]. Fourth, copeptin assay using its BRAHMs kryptor can give results within 19 minutes. This measurement tool is still in research step. Its cost may become reduced when introduced in clinical practice and globally distributed.

At the end, the assessment of copeptin cost effectiveness should be regional, in accordance to the regional prevalence of ED admitted patients with chest pain, the ED diagnostic guidelines, time factor and health care organization in the ED.

12. CONCLUSION

Activation of the HPA is the main physiological mechanism involved in adaptation for stress conditions, which involves rise in plasma AVP, CRH, ACTH and cortisol. Copeptin is a biological mirror for AVP that rises when AVP rises. So, copeptin accurately reflects plasma AVP level and enables clinical investigators to avoid the difficult and time wasting AVP assay techniques. AMI is a life threatening stress state in which the HPA is highly active. Early

identification of AMI among patients admitted to ED with acute chest pain remains a big problem due to the low sensitivity of electrocardiographic findings and delayed release of the most specific myocardial necrotic biomarkers, cTns. A multi-marker approach using two biomarkers of much distinct release pattern such as, the highly sensitive neuropeptide, copeptin as a marker of acute stress and representative for HPA together with the most specific markers for cardiac myocytes injury, cTns accelerates early differentiation between patients presenting with ischemic and non-ischemic chest pain and facilitates clinical decision for immediate medical intervention for ischemic chest pain patients and start of further investigations for non-ischemic chest pain patients. Thus, copeptin will be a promising biomarker in acute cardiac medicine if combined with cTns.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Brunton L, Chabner B, Knollman B, editors. Goodman and Gilamn's the pharmacological basis of therapeutics. 12th ed. China: McGrow-Hill companies; 2011.
2. Hammarsten O, Goetze PJ. Copeptin: A new peptide in clinical measurement. Kilnisk Niokemi I Norden. 2012;1:22-29.
3. Yalta K, Yalta T, Sirvi N, Yetkin E. Copeptin and cardiovascular disease: A review of a novel neurohormone. Inter J Cardiol. Online since Jan 2013. In press.
4. Holwerda DA. A glycopeptide from the posterior lobe of pig pituitaries. I. Isolation and characterization. Eur J Biochem. 1972;28:334-339.
5. Morgenthaler NG. Copeptin: A biomarker of cardiovascular and renal function. Congest Heart Fail. 2010;16(4)(suppl 1):S37-S44.
6. Khan SQ, Dhillon OS, O'Brien RJ, Struck J, Quinn PA, Morgenthaler NG, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. Circulation. 2007;115(16):2103-2110.
7. Mastropietro WC, MahanM, Valentine MK, Clark AJ, Hines CP, Walters III LH, et al. Copeptin as a marker of relative arginine vasopressin deficiency after pediatric cardiac surgery. Intensive Care Med. 2012;38:2047-2054.
8. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides. 2005;26:2500-2504.
9. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem. 2006;52(1):112-119.
10. Hanoune J. The neurohypophyseal system: synthesis and metabolism of vasopressin. In: Laycock J. F. Perspectives on vasopressin. London: *Imperical college press*; 2010.
11. Acher R, Chauvet J, Rouille Y. Dynamic processing of neuropeptides: sequential conformation shaping of neurohypophysial preprohormones during intraneuronal secretory transport. J Mol Neurosci. 2002;18:223-228.
12. Morgenthaler NG, Struck J, Jochberger S, Duser WM. Copeptin: clinical use of new biomarker. Trends Endocrinol Metabol. 2007;19:43-49.
13. Russell JT, Brownstein MJ, Gainer H. Biosynthesis of vasopressin, oxytocin and neurophysins: Isolation of two common precursors (propressophysin and prooxyphysin). Endocrinol. 1980;107:1880-1891.

14. Molina PE. Endocrine physiology. 3rd ed. USA; McGrow-Hill companies; 2010.
15. Vincent JL, Su F. Physiology and pathophysiology of the vasopressinergic system. Best Pract Res Clin Anaesthesiol. 2008;22(2):243-252.
16. Aguilera G. HPA axis responsiveness to stress: implications for healthy aging. Exp Gerontol. 2011;46(2-3):90-95.
17. Frank E, Landgraf R. The vasopressin system-from antidiuresis to psychopathology. Eur J Pharmacol. 2008;583(2-3):226-242.
18. Treschan TA, Peters J. The vasopressin system: physiology and clinical strategies. Anesthesiol. 2006;105(3):599-612.
19. Katoh K, Yoshida M, Kobayashi Y, Onodera M, Kogusa K, Obara Y. Responses induced by arginine-vasopressin injection in the plasma concentrations of adrenocorticotropic hormone, cortisol, growth hormone and metabolites around weaning time in goats. J Endocrinol. 2005;187(2):249-256.
20. Stevenson EL, Caldwell HK. The vasopressin 1b receptor and the neural regulation of social behavior. Horm Behav. 2012;61(3):277-282.
21. Maybauer MO, Maybauer DM, Enkhbaatar P, Traber DL. Physiology of the vasopressin receptors. Best Pract Res Clin Anaesthesiol. 2008;22(2):253-263.
22. Mannucci PM. Desmopressin: an historical introduction. Haemophilia. 2008;14(Suppl-1):1-4.
23. Nagy G, Mulchahey JJ, Smyth DG, Neill JD. The glycopeptide moiety of vasopressinneurophysin precursor is neurohypophysial prolactin releasing factor. Biochem. Biophys. Res. Commun. 1988;151:524-529.
24. Hyde JF, North WJ, Ben-Jonathan N. The vasopressin-associated glycopeptide is not a prolactin-releasing factor: studies with lactating Brattleboro rats. Endocrinol. 1989;125:35-40.
25. Szinnai G, Morgenthaler NG, Berneis K, Berneis K, Struck J, Müller B, et al. Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab. 2007;92(10):3973-3978.
26. Unic A, Rogic D, Rajsman G. Copeptin. Is there a role for another cardiac biomarker? J Med Biochem. 2011;30(3):224-229.
27. Williams DB. Beyond lectins: The calnexin/calreticulin chaperone system of the endoplasmic reticulum. J Cell Science. 2006;119:615-623.
28. Bhandari SS, Loke I, Davies JE, Squire IB, Struck J, Ng L. L. Gender and renal function influence plasma levels of copeptin in healthy individuals. Clin Sci (Lond). 2009;116:257-263.
29. Katan M, Morgenthaler NG, Dixit KC, Rutishauser J, Brabant GE, Müller B, et al. Anterior and posterior pituitary function testing with simultaneous insulin tolerance test and a novel copeptin assay. J Clin Endocrinol Metab. 2007;92:2640-2643.
30. Fenske W, Störk S, Blechschmidt A, Maier SG, Morgenthaler NG and Allolio B. Copeptin in the differential diagnosis of hyponatremia. J Clin Endocrinol Metab. 2009;94:123-129.
31. Jochberger S, Morgenthaler NG, Mayr VD, Luckner G, Wenzel V, Ulmer H, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. J Clin Endocrinol Metab. 2006;91(11):4381-4386.
32. Katan M, Christ-Crain M. The stress hormone copeptin: A new prognostic biomarker in acute illness. Swiss Med Wkly. 2010;140:w13101.
33. Kyrou I, Tsigos C. Stress hormones: Physiological stress and regulation of metabolism. Curr Opin Pharmacol. 2009;9(6):787-793.
34. De Kloet ER. From vasotocin to stress and cognition. Eur J Pharmacol. 2010;626(1):18-26.

35. Goodson JL, Kabelik D. Dynamic limbic networks and social diversity in vertebrates: from neural context to neuromodulatory patterning. Front Neuroendocrinol. 2009;30(4):429-441.
36. Katan M, Morgenthaler N, Widmer I, Puder JJ, König C, Müller B, et al. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett. 2008;29(3):341-346.
37. Enhörning S, Wang TJ, Nilsson PM, Almgren P, Hedblad B, Berglund G, et al. Plasma copeptin and the risk of diabetes mellitus. Circulation. 2010;121(19):2102-2108.
38. Enhörning S, Struck J, Wirfält E, Hedblad B, Morgenthaler NG, Melander O. Plasma copeptin, a unifying factor behind the metabolic syndrome. J Clin Endocrinol Metab. 2011;96(7):1065-1072.
39. Enhörning S, Bankir L, Bouby N, Struck J, Hedblad B, Persson M, et al. Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmö Diet and Cancer Study cardiovascular cohort. Int J Obes (Lond). 2013;37(4):598-603.
40. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med. 2012;10:7.
41. Sharma R, Kaddoura S. The definition and management of acute coronary syndrome. Cur Anaes Crit Care. 2005;16:305-312.
42. Leeper B, Cyr MA, Lambert C, Martin K. Acute coronary syndrome. Crit Care Nurs Clin N Am. 2011;23:547-557.
43. Boden H, van der Hoeven LB, Karalis I, Schalij JM, Jukema WJ. Management of acute coronary syndrome: achievements and goals still to pursue. Novel developments in diagnosis and treatment. J Intern Med. 2012;271:521-536.
44. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, Jr, et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2012;126(7):875-910.
45. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. The writing group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third international definition of myocardial infarction. Circulation. 2012;126:2020-2035.
46. Mueller C. Detection of myocardial infarction – Is it all troponin? Role of new markers. *Clin Chem*. 2012;58(1):162-164.
47. Keller T, Tzikas S, Zeller T, Czyz E, Lillpopp L, Ojeda MF, et al. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol. 2010;55(19):2096-2106.
48. Gu YL, Voors AA, Zijlstra F, Hillege HL, Struck J, Masson S, et al. Comparison of the temporal release pattern of copeptin with conventional biomarkers in acute myocardial infarction. Clin Res Cardiol. 2011;100:1069-1076.
49. Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, et al, the Study Group on Biomarkers in Cardiology of the ESCWorking Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J. 2010;31:2197-2204.
50. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthale NG, et al. Incremental value of copeptin for rapid role out of acute myocardial infarction. J Am Coll Cardiol. 2009;54:60-68.

51. Ray P, Charpentier S, Chenevier-Gobeaux C, Reichlin T, Twerenbold R, Claessens Y, et al. Combined copeptin and troponin to rule out myocardial infarction in patients with chest pain and history of coronary artery disease. Am J Emerg Med. 2012;30:440-448.
52. Chenvier-Gobeaux C, Freund Y, Claessens Y, Guerin S, Bonnet P, Doumenc B, Leumani F, et al. Copeptin for rapid rule out of acute myocardial infarction in emergency department. Inter J Cardiol. 2013;166(1):198-204.
53. Folli C, Consonni D, Spessot M, Salvini L, Velati M, Ranzani G, et al. Diagnostic role of copeptin in patients presenting with chest pain in the emergency room. Eur J Intern Med. 2013;24:189-193.
54. Lippi G, Plebani M, Di Somma S, Monzani V, Tubaro M, Volpe M, et al. Considerations for early acute myocardial infarction rule-out for emergency department chest pain patients: the case of copeptin. Clin Chem Lab Med. 2012;50(2):243-253.
55. Jerichow T, Struck J, Vollert LO, Vogt B, Mans D, Schroder M, et al. Elevation of plasma copeptin in acute myocardial infarction in pigs is related to changes in mean arterial blood pressure but not to myocardial ischemia. J Am Coll Cardiol. 2011;57(14):E925.
56. von Heahling S, Stojakovic T, Bigolake B. Copeptin – A novel biomarker in acute myocardial infarction. Clin Chem. 2012;58(1):307-308.
57. NICE medical technology guidance 4. BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain. NICE. 2011:1-19.
Available: http://guidance.nice.org.uk/mtg4.
58. Twerenbold R, Reichlin T, Reiter M, Meissner J, Heinisch C, Socrates T, et al. Economic benefit of copeptin for rapid rule out of acute myocardial infarction. Eur Heart J. 2010;31(Abstract Supplement):227-228.
59. Arias-Mendoza A, Bueno-Ayala L, Briseno-de la Cruz J, Sandoval-Zarate J, Gonzalez-Pacheco H, Martinez-Sanchez C. Usefullness of copeptin in the early diagnosis of acute coronary syndrome in the cardiovascular emergency department. J Am Coll Cardiol. 2013;61(10):E190.
60. Collinson PO, Gaze DC, Thokala P, Goodacre S. Randomised assessment of treatment using panel assay of cardiac markers – contemporary biomarker evaluation (RATPAC CBE). Health Technol Assess. 2013;17(15):1-144.

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