

The Clinical Value of Copeptin in Acute Coronary Syndrome

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Abstract

(1) The introduction of a novel immunoassay measuring copeptin, the c-terminal part of the vasopressin prohormone provided a unique window in common medical disorder. We examined the ability of copeptin in combination with cardiac troponin-I (cTn-I) in diagnosis of AMI, the differentiation between AMI and UA and finally evaluate the ability of copeptin in enhancing sensitivity of cTn-I at early hours of admission in emergency department.

(2) This study was carried on 50 subjects; they were divided into 33 patients with AMI and 17 patients with UA. Concentrations of copeptin, cTn-I and CK-MB were determined in their sera.

(3) In AMI group, the mean serum level of copeptin was highly significant in three hours than admission time and six hours. The mean serum level of cTn-I was highly significant in six hours than the admission time and three hours. The sensitivity and specificity of copeptin and cTn-I combination were 100% and 100% at the admission time versus 72.7% and 82.4% with cTn-I alone also versus 97% and 94.1% with combination of cTn-I and CK-MB. The AUC of the combination of copeptin and cTn-I was 1 which was significantly higher than the AUC of cTn-I alone 0.81 and the AUC of combination of cTn-I and CK-MB 0.92

(4) Copeptin as a single marker has diagnostic value being superior to cTn-I within the first three hours after acute chest pain. Dual marker strategy combining cTn-I and copeptin show incremental value in the early rule out of AMI.

Keywords: Acute Coronary Syndrome (ACS); AMI; Copeptin; Cardiac Troponin-I (cTn-I); CK-MB

Introduction

Acute coronary syndrome (ACS) encompasses a broad and heterogeneous population ranging from a patient with atypical chest discomfort, nonspecific electrocardiographic (ECG) changes, and normal cardiac biomarkers to the patient with a large ST-segment elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) [1].

Atherosclerosis is the underlying reason for nearly all causes of coronary artery disease, peripheral arterial disease and many cases of stroke. Atherosclerosis is a systemic inflammatory process characterized by the accumulation of lipids and macrophages/lymphocytes within the intima of large arteries [2].

Myocardial infarction; also known as heart attack, is defined in pathology as the death of cardiac muscle due to prolonged severe ischemia. The criteria meets the diagnosis when there is rise or fall in cTn-I with at least one value above the 99th percentile upper reference limit with symptoms of ischemia, ECG changes, Angiology [3].

Myocardial infarction can be recognized by clinical features, including ECG findings, elevated values of biochemical markers of myocardial necrosis and by imaging or may be defined by pathology [3].

Myocardial infarction can be classified into various types, based on pathological, clinical and prognostic differences, along with different treatment strategies [3].

Stable angina pectoris typically manifests as a deep, poorly localized chest or arm discomfort, reproducibly precipitated by physical exertion or emotional stress and relieved within 5 to 10 minutes by rest or sublingual nitroglycerin [4].

In contrast, UA is defined as angina pectoris or equivalent type of ischemic discomfort with at least one of three features: (1) occurring at rest or with minimal exertion and usually lasting >20 minutes; (2) being severe and usually described as frank pain; (3) occurring with a crescendo pattern [4].

Unstable angina can progress to NSTEMI and STEMI if left untreated. Unstable angina refers to a reduction in the blood flow in the coronary arteries typically caused by a rupture of atherosclerotic plaque leading to thrombus formation [5].

CKMB is an 86,000 Dalton is an enzyme that is predominantly located in myocardial cells and is released into the circulation in the setting of MI [6].

Troponins are structural and regulatory proteins of skeletal and cardiac muscle cells and are of essential importance in the regulation of muscle cell contraction. They were discovered in the 1970s and introduces to cardiology clinical practice in the late 1980s [7,8].

The Troponin protein complex is immobilized on the thin filament

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of the contractile apparatus of striated muscle. It consists of three distinct proteins encoded by separate genes which are troponin T, troponin I and troponin C [9].

Cardiac troponin I (cTnI) (molecular weight approximately 23 kDa) is a key regulatory protein in cardiac muscle contraction where it binds to actin in the thin myofilaments to hold the actin-tropomyosin complex in place and so the myosin cannot bind to actin in relaxed muscle. Proteolysis of cTnI and cTnT occurs in the myocardium in response to ischemia leading to post-translational modification [10-12].

Arginine vasopressin (AVP), also described as the antidiuretic hormone (ADH), is a nona peptide hormone with important osmoregulatory, hemodynamic, hemostatic, neuroendocrine and central nervous effects [13].

Copeptin was first time defined by Holwerda in 1972 [14], it is named as the C-terminal portion of provasopressin (cT-proVP) [15] and AVP associated glycopeptide. It is considered as a novel neurohormone (NH) of the AVP system which is co-secreted with AVP from hypothalamus [16].

Copeptin is a glycosylated 39 amino acid long peptide with leucine rich core segment [17-20]. Its molecular weight is 5000 Daltons (Da) [17,18].

Vasopressin is synthesized mainly in the perikarya of magnocellular neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus also in parvocellular neurons [19].

In humans, a 168-amino acid preprohormone is synthesized and a signal peptide (residues -23 to -1) ensures incorporation of the nascent polypeptide into ribosomes. During synthesis, the signal peptide is removed to form vasopressin prohormone which is processed and incorporated into the Golgi compartment and then into membrane-associated granules. The prohormone contains three domains: vasopressin (residues 1-9), vasopressin (VP)-neurophysin (residues 13-105) and copeptin (residues 107-145). The vasopressin domain is linked to the VP-neurophysin domain through a glycine-lysine-arginine-processing signal, and the VP-neurophysin is linked to the copeptin domain by an arginine-processing signal [19].

Clinical assay of plasma AVP is challenging due to multiple causes; AVP has a short plasma half-life (5-15 minutes), more than 90% of AVP in the circulation is bound to platelets resulting in underestimation of amounts of AVP actually released and it is highly unstable in vitro even at a temperature of -20°C due to its rapid biodegradation [13,16,18,20,21].

In addition to the time wasting analytical procedures (12-24 hours) needed to measure AVP also a careful sample handling, sample extraction is needed and an addition of protease inhibitors [22,23].

Because of the small size of AVP; so the ability to be measured by the more accurate sandwich enzyme linked immunoassay (ELISA) is impossible. This factor enforced the use of less sensitive competitive immunoassay [13].

Copeptin seems to be an ideal shadow for AVP in clinical assessment due to the 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°C [13,20,24].

Copeptin assay techniques need no special handling precautions

for samples and could be done on both plasma and serum using minute volume of samples (50 µL) versus 1 mL for AVP. Copeptin assay is faster and the results are available within 1-5.5 hours according to the analytical method [13,18].

Subjects and Methods

This study was carried on 50 subjects suffering from acute chest pain attending the National Heart Institute, in the period from February till July 2012. They were divided into two groups:

- (I) Acute Myocardial infarction group: comprised 33 diagnosed as AMI of age (47-73 years) with mean (58.9 ± 1.11 years) and BMI of range (23.2-39.1 Kg/m²) with mean (30.2 ± 0.75 Kg/m²), 22 were males and 11 were females.
- (II) Unstable Angina group: comprised 17 patients diagnosed as UA of age (49-71 years) with mean (59.2 ± 1.46 years) and BMI of range (23.5-38.9 Kg/m²) with mean (30.6 ± 1.08 Kg/m²), 11 were males and 6 were females

This study has been cleared by our Institution Ethics Review Board for human studies and that the patients have signed an informed consent.

Eligible patients were selected according to the following inclusion and exclusion criteria:

Inclusion criteria:

All patients admitted to the ED of the NHI suffering from acute chest pain within 3 hours from the admission time and their clinical findings revealed ACS

Exclusion criteria:

- (1) All patients with positive ECG abnormalities
- (2) All patients were using medications which can affect plasma AVP level.
- (3) All patients with other diseases that may alter normal patterns of AVP release as in acute or chronic renal failure, end stage liver diseases, systemic infections and chronic obstructive pulmonary disease.

Copeptin was measured using ELISA technique using Phoenix Pharmaceuticals, inc: USA, according to the principle of Porstmann and Kiessig et al. [25].

Cardiac troponin-I was measured using ELISA technique using Monobind Inc: USA, according to the principle of Apple et al. [26]. CK-MB was measured using photometer 5010 using Stanbio: USA, according to the principle of Dawson et al. [27].

Statistical methods

- (1) Graph pad prism program version 5.0 was used for analysis of all the data.
- (2) Data were summarized as mean ± SEM; Paired, non-parametric Wilcoxon test was used for analysis of two quantitative data.
- (3) Non parametric Fried man's test was used for analysis of more than two quantitative data followed by Dunns for detection of significance.

P-value was considered significant if <0.05.

- (4) Mac Apple Epi-Stat S3A Pro statistics package (V. 4.0, Apple

Corp., USA, 2012) was used for data analysis. Diagnostic validity test was done: It includes: diagnostic specificity, diagnostic specificity, positive predictive value (PPV) and negative predictive value (NPV). The receiver operator characteristic (ROC) curve was constructed to obtain the most sensitive and specific cutoff for each technique. To evaluate the most discriminating markers between the compared groups, area under ROC curve can also be calculated. Multi-ROC or combination between more than 1 parameter was used

Results

Table 1 and Figure 1 showed that the mean serum level of copeptin was highly significant increased in three hours of AMI group than the admission time and six hours at $P < 0.001$.

Table 2 and Figure 2 showed that the mean serum level of cTn-I was highly significant increased in six hours of the AMI group than the admission time and three hours at $P < 0.001$. Also the mean serum level of cTn-I was significantly increased in three hours of the AMI group than the admission time at $P < 0.001$.

Table 3 and Figure 3 showed that the mean serum level of CK-MB was highly significant in three and six hours of AMI group than the admission time at $P < 0.001$. Also the mean serum level of CK-MB was highly significant in six hours than the three hours at $P < 0.001$.

Regarding the mean serum copeptin value in UA group, a non-significant difference was found between the three time intervals as shown in Table 4 and Figure 4.

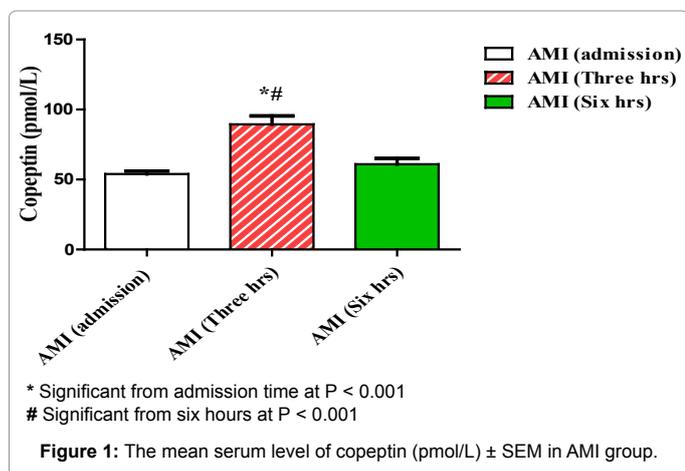
Table 5 and Figure 5 showed that the mean serum level of cTn-I (ng/mL) was significantly increased in three and six hours of the UA group than the admission time at $P < 0.001$ also the mean serum level of cTn-I was highly significant increased in six hours than the three hours at $P < 0.001$.

Regarding the mean serum level of CK-MB was highly significant increased in three and six hours of the UA group than the admission time at $P < 0.001$ also the mean serum level of CK-MB was highly

Time of admission (hour)	No. of cases	Range	Mean \pm SEM
Admission	33	22.4-83.4	54.0 \pm 2.13
Three	33	37.3-213	89.5 \pm 5.93*#
Six	33	13.6-113	60.9 \pm 4.19

*Significant from admission time at $P < 0.001$.
#Significant from six hours at $P < 0.001$.

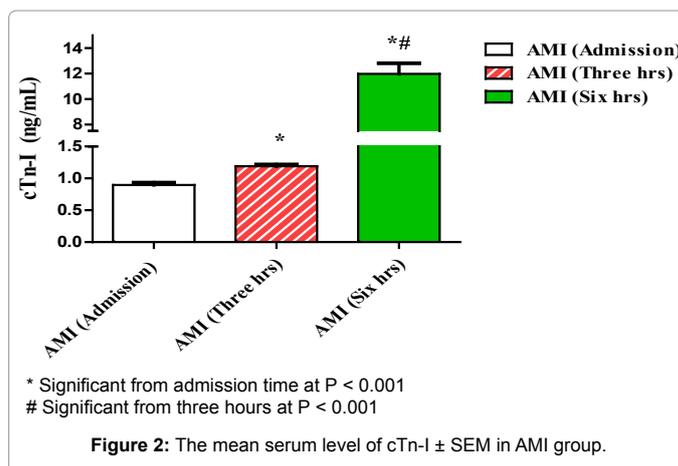
Table 1: Serum copeptin (pmol/L) in AMI group.



Time of admission (hour)	No. of cases	Range	Mean \pm SEM
Admission	33	0.37-1.23	0.89 \pm 0.03
Three	33	0.98-1.58	1.19 \pm 0.02
Six	33	4.78-23.3	12.0 \pm 0.83*#

*Significant from admission time at $P < 0.001$.
#Significant from three hours at $P < 0.001$.

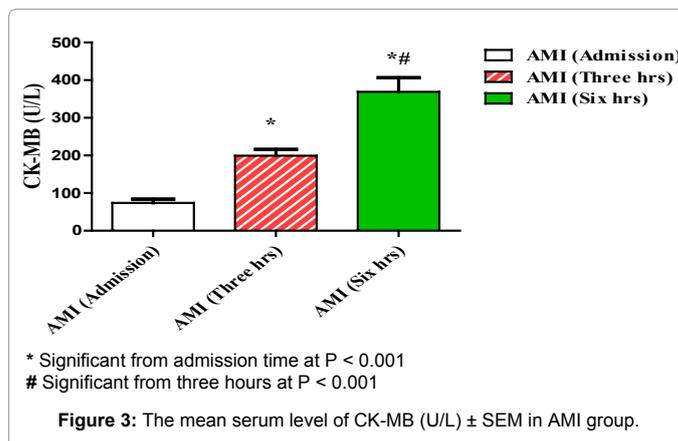
Table 2: Serum cTn-I (ng/mL) in AMI group.



Time of admission (hour)	No. of cases	Range	Mean \pm SEM
Admission	33	8-244	73.8 \pm 10.1
Three	33	54-436	199 \pm 16.4*
Six	33	66-1020	369 \pm 37.1*#

*Significant from admission time at $P < 0.001$.
#Significant from three hours at $P < 0.001$.

Table 3: Serum CK-MB (U/L) in AMI group.



significant increased in six hours than the three hours at $P < 0.001$ as shown in Table 6 and Figure 6.

In relation to the representative time courses of copeptin, cTn-I and CK-MB in patients suffering from AMI and UA during the first six hours after admission it was found that the mean serum copeptin level seemed to be increased during the first three hours and then decline afterward at $P < 0.001$, by contrast the mean cTn-I levels strongly increased within six hours after admission at $P < 0.001$ whereas the mean CK-MB concentration continuously increased within the observed six hours at $P < 0.001$ in AMI group as shown in Figures 7-9.

Time of admission (hour)	No. of cases	Range	Mean ± SEM
Admission	17	3.59-49.9	12.7 ± 2.96
Three	17	3.18-74.8	16.9 ± 5.43
Six	17	3.46-41.4	12.5 ± 2.93

Table 4: Serum copeptin (pmol/L) in UA group.

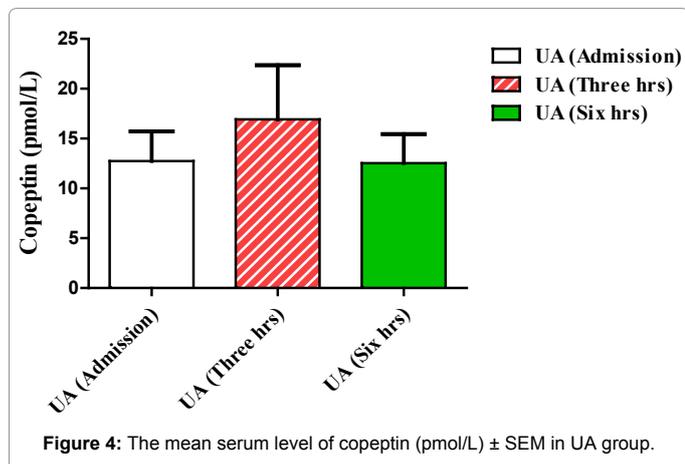


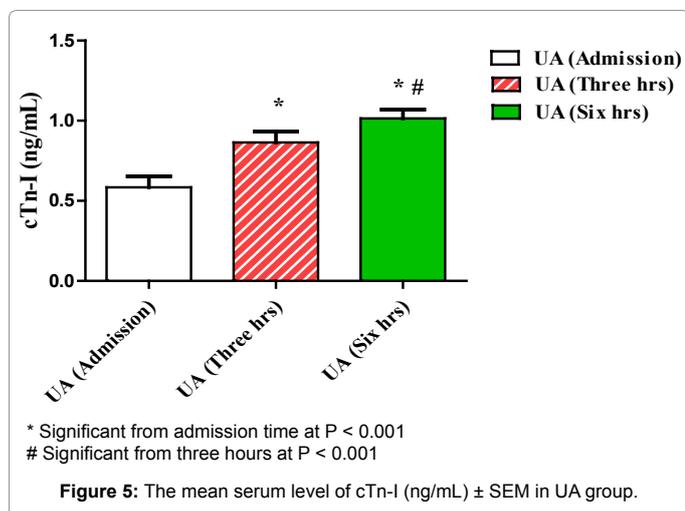
Figure 4: The mean serum level of copeptin (pmol/L) ± SEM in UA group.

Time of admission (hour)	No. of cases	Range	Mean ± SEM
Admission	17	0.21-1.07	0.58 ± 0.06
Three	17	0.24-1.17	0.86 ± 0.06*
Six	17	0.40-1.22	1.01 ± 0.05*#

*Significant from admission time at P<0.001.

#Significant from three hours at P<0.001.

Table 5: Serum cTn-I (ng/mL) in UA group.



* Significant from admission time at P < 0.001

Significant from three hours at P < 0.001

Figure 5: The mean serum level of cTn-I (ng/mL) ± SEM in UA group.

Time of admission (hour)	No. of cases	Range	Mean ± SEM
Admission	17	2-80	32 ± 5.75
Three	17	20-338	126 ± 19.8*
Six	17	54-448	189 ± 28.3*#

*Significant from admission time at P<0.001.

#Significant from three hours at P<0.001.

Table 6: Serum CK-MB (U/L) in UA group.

While in UA group, it was found that copeptin and cTn-I levels remained unchanged within six hours after admission while the mean CK-MB concentration continuously increased within the observed six hours at P<0.001 as shown in Figures 7-9.

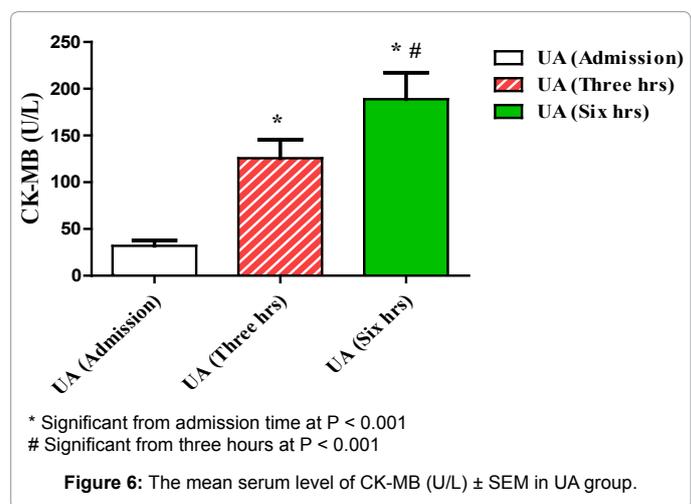
It was cleared from Table 7 and Figure 10 that copeptin value 30.7 can be used as a cut-off point at which 93.9% of the AMI patients can be diagnosed correctly but 5.90% of normal persons are false positive. According to the ROC curve, the sensitivity was 93.9% while the specificity was 94.1%.

Regarding cTn-I, it was found from Table 7 and Figure 10 that cTn-I value 0.87 can be used as a cut-off point at which 72.7% of the AMI patients can be diagnosed correctly but 17.6% of normal persons are false positive. According to the ROC curve, the sensitivity was 72.7% while the specificity was 82.4%.

While CK-MB, it was found from Table 7 and Figure 10 that CK-MB no. 32 can be used as a cut-off point at which 66.7% of the AMI patients can be diagnosed correctly but 29.4% of normal persons are false positive. According to the ROC curve, the sensitivity was 66.7% while the specificity was 70.6%.

It was cleared from Table 8 and Figure 11 that copeptin value 51.7 can be used as a cut-off point at which 97% of the AMI patients can be diagnosed correctly and 11.8% of normal persons are false positive. According to the ROC curve, the sensitivity was 97% while the specificity was 88.2%.

Regarding cTn-I, it was found from Table 8 and Figure 11 that cTn-I value 1.017 can be used as a cut-off point at which 90.9% of the AMI patients can be diagnosed correctly but 35.3% of normal persons are false positive. According to the ROC curve, the sensitivity was 90.9% while the specificity was 64.7%.



* Significant from admission time at P < 0.001

Significant from three hours at P < 0.001

Figure 6: The mean serum level of CK-MB (U/L) ± SEM in UA group.

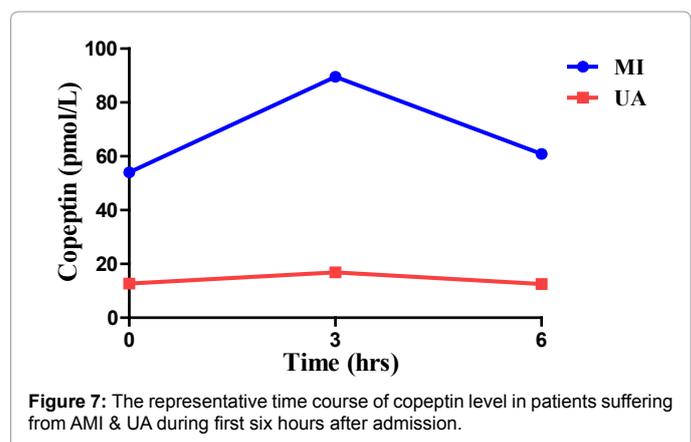


Figure 7: The representative time course of copeptin level in patients suffering from AMI & UA during first six hours after admission.

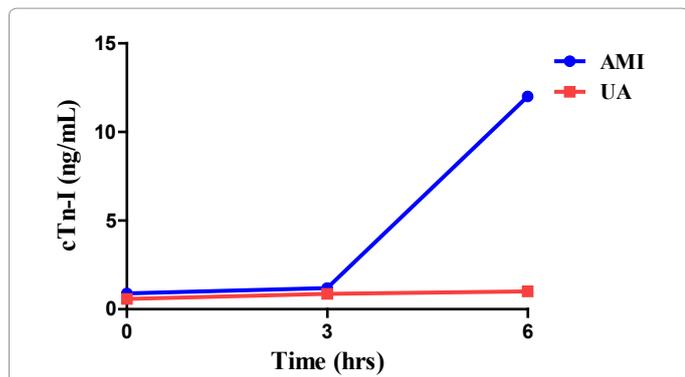


Figure 8: The representative time course of cTn-I level in patients suffering from AMI & UA during first six hours after admission.

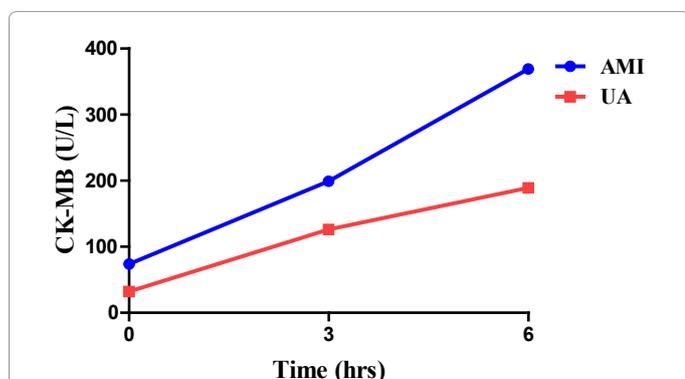


Figure 9: The representative time course of CK-MB level in patients suffering from AMI & UA during first six hours after admission.

Variable	Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
Copeptin	30.7	93.9	94.1	88.9	96.9	0.98
cTn-I	0.87	72.7	82.4	60.9	88.9	0.81
CK-MB	32	66.7	70.6	52.2	81.5	0.77

Table 7: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of copeptin, cTn-I and CK-MB at admission time.

While CK-MB, it was found from Table 8 and Figure 11 that CK-MB no. 146 can be used as a cut-off point at which 69.7% of the AMI patients can be diagnosed correctly but 35.3% of normal persons are false positive. According to the ROC curve, the sensitivity was 69.7% while the specificity was 64.7%.

It was cleared from Table 9 and Figure 12 that copeptin value 30.7 used as a cut-off point with cTn-I value 0.58 at which 100% of the AMI patients can be diagnosed correctly and no false positive. According to the ROC curve, the sensitivity was 100% while the specificity was 100%.

Regarding cTn-I with CK-MB, it was found from Table 10 and Figure 12 that cTn-I value 0.87 used as a cut-off point with CK-MB value 18 at which 97% of the AMI patients can be diagnosed correctly but 5.9% of normal persons are false positive. According to the ROC curve, the sensitivity was 97% while the specificity was 94.1%.

It was cleared from Table 11 and Figure 13 that copeptin value 51.7 used as a cut-off point with cTn-I value 1.01 at which 100% of the AMI patients can be diagnosed correctly and no false positive. According to the ROC curve, the sensitivity was 100% while the specificity was 100%.

Regarding cTn-I with CK-MB, it was found from Table 12 and

Figure 13 that cTn-I value 1.017 used as a cut-off point with CK-MB value 146 at which 97% of the AMI patients can be diagnosed correctly and no false positive. According to the ROC curve, the sensitivity was 97% while the specificity was 100%.

Discussion

The elevation of copeptin in the AMI group during the first three hours may be due to two hypothesis; first the stress hypothesis where copeptin/AVP is a substantial part of the endocrine stress response resulting in a synergistic release of ACTH and cortisol. While the second is the hemodynamic hypothesis where AMI results in cardiac underfilling leading to baroreceptor stimulation and finally secretion of copeptin/AVP from the posterior pituitary [28].

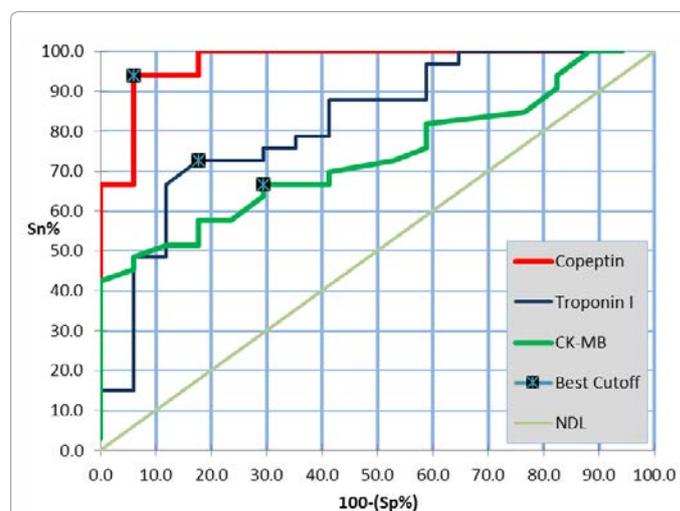


Figure 10: The ROC curve of copeptin, cTn-I and CK-MB at admission time.

Variable	Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
Copeptin	51.7	97	88.2	93.8	94.1	0.98
cTn-I	1.017	90.9	64.7	78.6	83.3	0.81
CK-MB	146	69.7	64.7	52.4	79.3	0.77

Table 8: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of copeptin, cTn-I and CK-MB at three hours.

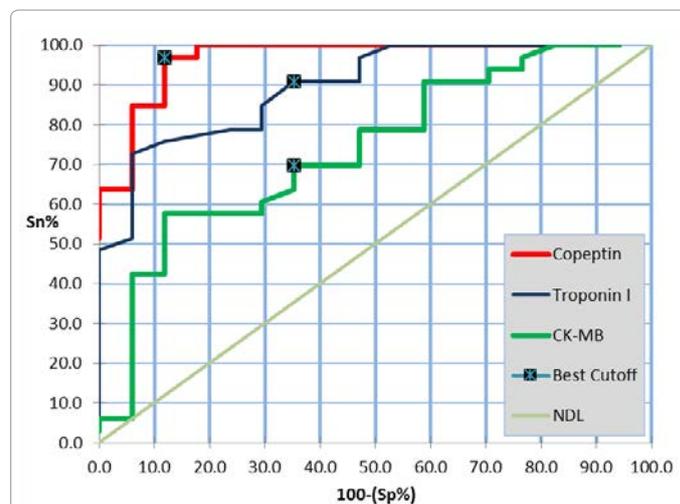


Figure 11: The ROC curve of copeptin, cTn-I and CK-MB at three hours.

Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
0.58	100	100	100	100	1

Table 9: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of copeptin at 30.7 with cTn-I at admission time at.

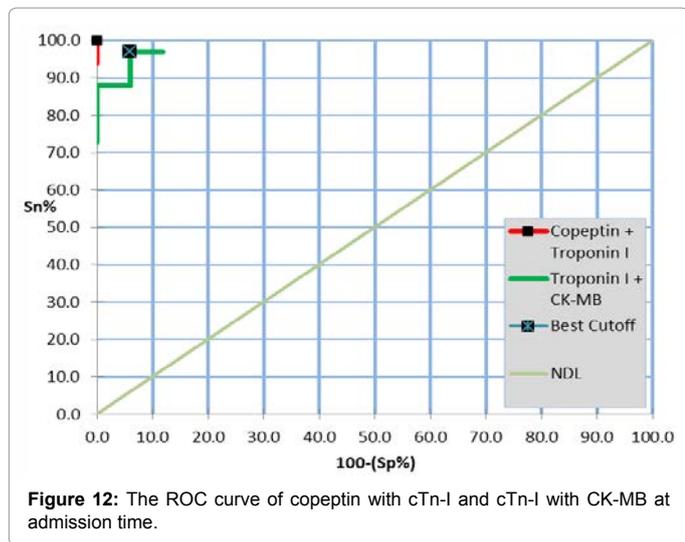


Figure 12: The ROC curve of copeptin with cTn-I and cTn-I with CK-MB at admission time.

Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
18	97	94.1	94.1	97	0.92

Table 10: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of cTn-I at 0.87 with CK-MB at admission time at.

Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
1.01	100	100	100	100	1

Table 11: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of copeptin at 51.7 with cTn-I at three hours at.

While the decline of copeptin afterwards may be due to the initiation of the formation of new angiogenesis of collateral coronaries which may reduce the ischemic symptoms, decrease the stimulation of cardiac baroreceptors and consequently decrease the copeptin/AVP release axis.

These results were in accordance with Reichlin et al., Keller et al., Charpentier et al. and Folli et al. where copeptin levels at admission were higher in the AMI group presenting zero to four hours after onset of symptoms with a falling pattern afterward from five to ten hours [29-32].

In relation to cTn-I, White, 2011 suggested six potential pathobiological mechanisms for troponin elevations: Myocyte necrosis, apoptosis, normal myocyte turnover, cellular release of proteolytic troponin degradation products, increased cell membrane permeability, formation and release of membranous blebs [33].

The gradual increase of cTn-I may be due to majority of cTn-I is bound to myofilaments while the remainder is free in the cytosol. When myocyte damage occurs; the cytosolic pool is released first followed by a more protracted release from stores bound to deteriorating myofilaments [34].

In accordance with these results a study was carried out by Charpentier et al. and Chenevier-Gobeaux et al. where cTn-I level showed a delayed increase after admission of patients with AMI [31,35].

The gradual increase in the level of CK-MB in AMI group in this

study may be due to its location predominantly in a cytoplasmic pool of myocardial cells therefore after disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first.

These results agree with a study carried out by Esses et al. where CK-MB was measured on admission, six, twelve, eighteen in which a gradual increase in its level in MI group.

Regarding the mean serum copeptin value in UA group, a non-significant difference was found between the different time intervals [36]. These results may be due to partial occlusion (obstruction) in coronaries therefore there is a minimal oxygen supply as a result no cardiac underfilling, so no baroreceptors stimulation leading to no release of copeptin/AVP.

In accordance with these results a study carried by Reichlin et al., Keller et al., Charpentier et al., and Folli et al., in which the copeptin values of UA subset of patients with ACS were normal and didn't show any difference from those observed in patients with benign causes of chest pain [29-32].

In UA, there is no trigger for cTn-I release as the cardiac myocyte still intact without any pathological necrosis but the presence of minute amounts of serum cTn-I in the UA group may be due to the normal turnover rate of cardiac myocytes. According to these results the mean serum level of cTn-I didn't reach the cutoff value for the different time intervals.

Regarding the mean serum level of CK-MB was highly significant in three and six hours of UA group than the admission time at $P < 0.001$ also the mean serum level of CK-MB was highly significant in six hours than the three hour at $P < 0.001$.

The increased level of CK-MB in UA group may be due to its release secondary to coronary obstruction, other forms of injury to cardiac muscle; such as those resulting from myocarditis, trauma, cardiac catheterization, shock and cardiac surgery.

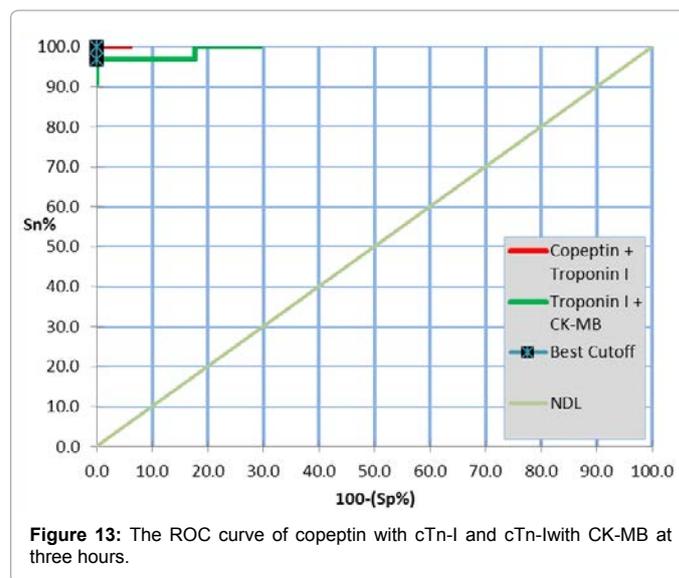


Figure 13: The ROC curve of copeptin with cTn-I and cTn-I with CK-MB at three hours.

Cutoff	Sensitivity%	Specificity%	NPV%	PPV%	Area
146	97	100	94.4	100	0.97

Table 12: The cutoff, sensitivity, specificity, NPV, PPV and area under ROC curve of cTn-I at 1.017 with CK-MB at three hours at.

Early identification of patients at risk in a population with undifferentiated chest pain is essential since these patients need an aggressive therapeutic regimen [30].

At admission time; cTn-I with cutoff value of 0.87 ng/mL revealed AUC=0.81, with sensitivity 72.7%, specificity 82.4%, NPV 60.9% and PPV 88.9%, while copeptin diagnostic accuracy at the same time at cutoff value of 30.7 pmol/L was much higher than that of cTn-I with AUC=0.98, with sensitivity 93.9%, specificity 94.1%, NPV 88.9%, PPV 96.9%, so copeptin was more sensitive and specific than cTn-I with better NPV and PPV.

These results were in accordance with Keller et al. and Ray et al. [30,37].

Using the dual marker strategy, involving the different pathophysiological basis of release of cTn-I as the most specific biomarker for cardiomyocytes injury and copeptin as indicator for stress and hemodynamic instability; theoretically it would provide more accurate diagnostic performance.

When both ROC of cTn-I and copeptin were merged together at the admission time, a positive impact on diagnostic performance was improved reaching AUC of 1.00, sensitivity 100%, Specificity 100%, NPV 100% and PPV 100% at cutoff value for copeptin 30.7 pmol/L and cut-off value for cTn-I 0.58 ng/mL

These results were in accordance with Reichlin et al., Keller et al., Charpentier et al. and Ray et al., [29-31,37].

At the admission time; CK-MB with cutoff value of 32 U/L revealed AUC=0.77, with sensitivity 66.7%, specificity 70.6%, NPV 52.2% and PPV 81.5%.

However upon combination of both cTn-I and CK-MB at admission time, the AUC was 0.92 with sensitivity 97%, specificity 94.1%, NPV 94.1% and PPV 97% at cutoff value for cTn-I 0.87 ng/mL and for CK-MB 18 U/L.

In spite of the obvious added diagnostic value of CK-MB to cTn-I at admission time; but it was still lower than that of copeptin and cTn-I combination.

At three hours; cTn-I with cutoff value of 1.017 ng/mL revealed AUC=0.93, with sensitivity 90.9%, specificity 64.7, NPV 78.6% and PPV 83.3%, while copeptin diagnostic accuracy at the same time at cutoff value of 51.7 pmol/L was much higher than that of cTn-I with AUC=0.97, with sensitivity 97%, specificity 88.2%, NPV 93.8%, PPV 94.1%, so copeptin was more sensitive and specific than cTn-I with better NPV and PPV.

When both ROC of cTn-I and copeptin were combined together at three hours, a positive impact on diagnostic performance was improved reaching AUC of 1.00, sensitivity 100%, Specificity 100%, NPV 100% and PPV 100% at cutoff value for copeptin 51.7 pmol/L and cut-off value for cTn-I 1.01 ng/mL

These results were in accordance with Reichlin et al., Keller et al. [29,30].

At the three hours; CK-MB with cutoff value of 146 U/L revealed AUC=0.73, with sensitivity 69.7%, specificity 64.7%, NPV 52.4% and PPV 79.3%.

However upon combination of both cTn-I and CK-MB at three hours, the AUC was 0.97 with sensitivity 97%, specificity 100%, NPV

94.4% and PPV 100% at cutoff value for cTn-I 1.017 ng/mL and for CK-MB 146 U/L.

This combination provide a higher specificity and PPV than that at admission time

In spite of the obvious added diagnostic value of CK-MB to cTn-I at three hours; but it was still lower than that of copeptin and cTn-I combination.

Conclusion

- (1) The introduction of a novel immunoassay measuring copeptin, the c-terminal part of the vasopressin prohormone provided a unique window into the role of this system in common medical disorder.
- (2) Determination of copeptin as a single marker has diagnostic value being superior to a conventional cTn-I within the first three hours after acute chest pain but still single copeptin determination unable to displace or challenge a serial cTn-I measurement to detect myocardial necrosis within a rule-in approach.
- (3) The improvement in the early rule out of AMI offered by copeptin testing may have the potential to improve allocation of resources in the emergency department and markedly reduce total treatment cost.
- (4) Our data suggest that a dual marker strategy combining cTn-I and copeptin benefits from the integration of complementary information provided by pathophysiologically different processes: cTn-I for the detection and quantification of myocardial necrosis, and copeptin for the quantification of endogenous stress show incremental value in the early rule out of AMI with high NPV.
- (5) The combination of copeptin and cTn-I has higher diagnostic accuracy than that of cTn-I and CK-MB.

As per this conclusion, copeptin is considered to be an important biomarker in diagnosing acute myocardial infarction which should be applicable in the daily work not only the experimental field.

Study Limitations

The following limitations of the present study have to be addressed.

First, our study is limited by the enrollment of a limited number of patients included from single recruiting medical center (single center study). The results, therefore, are preliminary and need to be confirmed and extended in larger multicenter studies on a larger number of the population to get more valid and reliable cutoff values and diagnostic impact.

Second, in this study, patients having STEMI were excluded which precluded the differentiation of the clinical values and release pattern of copeptin in the three categories of ACS; STEMI, NSTEMI and UA.

Third, this study was only observational and cannot quantify exactly the clinical benefits associated with the combination of copeptin and cTnI since no clinical decision or pathway was based on Copeptin values. Thus, further randomized interventional studies are required to obtain this information.

Fourth, the use of conventional cTnI assay instead of the newest generation of high sensitivity cTnI and the use of a spectrophotometric method for CK-MB instead of the recommended mass detecting

techniques as ELISA or gel electrophoresis were due to two causes. One of them related to the cost effectiveness of the study as it was self-funded, while the second was to mimic the actual diagnostic tools applied in Egypt, where both cTnI and CK-MB are usually detected using the mentioned methods.

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Conflict of Interest

There is no conflict of interest.

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