

Copeptin as Early Marker of Acute Non-ST Elevation Myocardial Infarction in Patients Suspected with Acute Coronary Syndrome

Samir Rafla^{1*}, Mohamed Sadaka¹, Sahar Azab¹, Eman Soliman² and Samy Soliman Fahim³

¹Cardiology Department, Faculty of Medicine, Alexandria University, Egypt

²Clinical Pathology Department, Faculty of Medicine, Alexandria University, Egypt

³Ministry of Health, Faculty of Medicine, Alexandria University, Egypt

*Corresponding Author: Samir Rafla, Cardiology Department, Faculty of Medicine, Alexandria University, Egypt.

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Abstract

Background: Rapid diagnosis and management of AMI have great impact on morbidity and mortality. Diagnosis which is based on elevation of cardiac biomarkers has its limitations. One of the major limitations is the delayed release in circulation. So, looking for a new marker with a short diagnostic time window is needed. Copeptin is the c-terminal part of the vasopressin prohormone. The pathophysiology mode of release should theoretically add diagnostic information of cardiac cell necrosis. Aim is to determine the role of copeptin as an early marker for acute non-ST elevation MI (NSTEMI).

Methods: This study included 88 patients with chest pain. They were divided into 2 groups. Group (1); included 30 patients with diagnosis of NSTEMI. Diagnosis of AMI was established according to the universal definition of MI. Group (2); included 58 patients with diagnosis of unstable angina (UA). Full medical history, physical examination, 12 lead ECG, random blood glucose level, renal function, total cholesterol, triglyceride, cardiac troponin I and Copeptin were obtained on admission. Follow up cardiac troponin I was done. Inclusion criteria: Defined as chest pain of ≤ 6 hour duration since onset, suggestive of myocardial ischemia, and lasting > 20 minutes at rest. Exclusion criteria: Patients with positive First cardiac troponin were rolled out, patients with ST segment elevation were rolled out. Other exclusion criteria: Patients presenting after a cardiac arrest, Trauma or major surgery within the last 4 weeks; pregnancy; IV drug abuse; age less than 18 years; shock and sepsis. Patients who were included had second troponin I re-done and copeptin analysis done. In group 1 (NSTEMI) 28 patients had ECG changes and only 2 had NSTEMI without ECG changes. In group 2 (UA) 23 patients had ECG changes and 35 patients had normal ECG.

Results: Males and females were 49 and 39. Age in G1 and G2 was 60 +/- 4 and 53 +/- 5. Copeptin analysis was done 6 hours after Infarction or chest pain. All the patients with NSTEMI (30) had positive copeptin and positive troponin except one only who had + Troponin only and another one who had + copeptin only. Of the 58 patients without MI none had the two tests positive, only one had + troponin and one had + copeptin. Using ROC curve: copeptin had sensitivity 100% and specificity 82.8% with using cut off point 13.2 pmol/l. So copeptin can be used for early detection of myocardial infarction.

Conclusion: Copeptin seems to be an ideal confirmatory marker for rapid rule out of AMI. If the two tests (with troponin) are positive, this is evident MI; if the two are negative it rules out MI.

Keywords: Copeptin; Myocardial Infarction; Acute Coronary Syndrome

Introduction

Acute myocardial infarction (AMI) is the major cause of death and disability worldwide, with an ongoing increase in incidence. Approximately 15 million patients per year present to the emergency department (ED) with chest pain or other symptoms suggestive of AMI in the U.S. and Europe. Nawar, *et al.* [1] rapid assessment of these patients is critical to direct further diagnostic and therapeutic strategies. The vast majority of patients presenting to the ED with suspected AMI, however, finally prove not to have AMI. Current rule out of AMI is time-consuming and expensive. Peacock [2]. One-quarter to one-third of patients with AMI present without significant ECG changes indicative of acute ischemia.

Criteria for Acute, Evolving, or Recent MI

Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI:

Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following:

- a. Ischemic symptoms.
- b. Development of pathological Q waves in the ECG.
- c. ECG changes indicative of ischemia (ST segment elevation or depression).
- d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Cardiac biomarkers

Because the diagnosis of NSTEMI implies ischemia severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury Kristian Thygesen, *et al.* [3]. It is important to discuss the different cardiac markers of injury. Biochemical markers such as troponins, creatinine kinase, and myoglobin are useful both prognostically and for the diagnosis of myonecrosis.

Favorable biomarker features Wu, *et al* [4].

1. High concentrations in myocardium.
2. Absent in non-myocardial tissue.
3. Release in to blood within a convenient diagnostic time window.
4. Release in proportion to the extent of myocardial injury.
5. Inexpensive.
6. Easily applied assay.
7. Stable *in vitro*.
8. Predict prognosis.
9. Widely available.

Creatine kinase

CK-MB is less sensitive and specific for MI than the cardiac troponins, however it remains useful for the diagnosis of early infarct extension (reinfarction) and periprocedural MI because its short half-life better permits the detection of secondary increases in marker levels.

Myoglobin

Because of its lack of cardiac specificity, an isolated measurement of myoglobin within the first 4 to 8 hours after the onset of chest discomfort in patients with a non-diagnostic ECG should not be relied on to make the diagnosis of MI [5].

Troponins

The cardiac troponins are sensitive and specific markers of myocyte necrosis [6] and are the markers of choice for the diagnosis of MI.

Limitations of cardiac troponin

In patients with renal failure, spurious cTn-T elevation and CK-MB have been found [7]. Studies have shown that cTn-I accurately predicts myocardial injury in patients with renal failure.

Multiple acute illnesses besides myocardial infarction may cause cardiac injury and lead to troponin elevation. Moreover, in the general population, diabetes, left ventricular hypertrophy, left ventricular dysfunction or heart failure, and moderate or severe renal insufficiency may be associated with chronic cTnT elevation, even in the absence of signs and symptoms of ischemia [8].

Advantages of highly sensitive troponin in comparison to conventional assay

1. Early diagnosis
2. Presence of prognostic value.

Need for new cardiac biomarker

Current markers of necrosis leak from cardiomyocytes after the loss of membrane integrity and diffuse into the cardiac interstitial, then into the lymphatics and cardiac microvasculature. Eventually, these macromolecules, collectively referred to as cardiac biomarkers, are detectable in the peripheral circulation, so looking for a marker of different mode of release should theoretically add diagnostic information.

Copeptin

Copeptin is the c-terminal part of the vasopressin prohormone and is equimolar to vasopressin (AVP).

Mechanism by which AVP/copeptin increase after MI

AVP is a substantial part of the endocrine stress response, resulting in ACTH and cortisol release.

Other causes of increase copeptin level other than myocardial infarction

Heart failure: sympathetic and renin-angiotensin system activation in heart failure override the volume and low pressure cardiovascular receptors and cause an increase in copeptin secretion. Copeptin level increases in different states of shock [9]. Copeptin increase in patients with community-acquired pneumonia, exacerbated chronic obstructive pulmonary disease, and sepsis.

Aim of the Work

The study is designed to determine the role of copeptin as an early marker for acute myocardial infarction

Materials and Methods

Patients

After approval of Ethics Committee of the faculty of medicine and with written informed consent, the present study was carried out in the cardiology department of Alexandria Main University Hospital on 88 patients admitted to the coronary care unit (CCU).

All patients given a written informed consent to be in the study which was divided to three phases:

- **Phase A:** Upon admission to the hospital, all patients underwent a detailed Clinical evaluation, including medical history, 12-lead ECG, Continuous bedside ECG monitoring, screening blood tests.
- **Phase B:** Conventional cardiac troponin I assay and copeptin on admission.
- **Phase C:** Follow up after 6 hours cardiac troponin I and ECG to establish the diagnosis.

The study included 88 patients: group 1 was 30 patients who had a diagnosis of NSTEMI while group 2 was 58 patients who had a diagnosis of unstable angina.

Inclusion criteria: Defined as chest pain of ≤ 6 hours duration since onset, suggestive of myocardial ischemia, and lasting > 20 minutes at rest.

Exclusion criteria: 1. Patients presenting after a cardiac arrest. 2. Trauma or major surgery within the last 4 weeks. 3. Pregnancy. 4. Intravenous drug abuse. 5. Age less than 18 years. 6. Shock. 7. Sepsis. 8. First cardiac troponin is positive. 9. ST segment elevation on ECG.

Methods

This study included all patients coming to emergency department (ER) complaining of typical chest pain that require admission to intensive care unit (ICU). ECG was done and patients with raised ST segment were rolled out from the study. Cardiac troponin I was done on admission (first round) and patients with positive results were rolled out too.

Patients with non ST segment elevation in ECG and their first cardiac Troponin I test are negative was rolled in the study.

All patients were subjected to: Thorough history taking with special emphasis on: Age, Sex. Preexisting medical conditions: Hypertension, Diabetes mellitus, Drug history, Analysis of chest pain, Special habits: smoking.

1. Clinical examination:
2. Standard 12 lead ECG.

Laboratory investigations: Random blood glucose level. Renal function testes: urea and creatinine. Total cholesterol and triglyceride. Conventional cardiac troponin I assay by immunoassay based on the sandwich principle [10].

Cardiac Troponin I one-step enzyme immunoassay system (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA). The measurement range extended from 0.04 to 40.00 $\mu\text{g/L}$. Analytic sensitivity is 0.04 $\mu\text{g/L}$ this represent the lowest concentration of cardiac troponin-I that can be distinguished from zero. Results less than 0.04 $\mu\text{g/L}$ should be reported as less than 0.04 $\mu\text{g/L}$ instead of numerical value, while results more than 40 $\mu\text{g/L}$ should be repeated on dilution. The threshold for this method (0.14 $\mu\text{g/L}$) corresponds to the lowest substrate concentration that can be reproducibly measured with a $\text{CV} \leq 10\%$ would be ideal [10].

Copeptin by immunoassay based on the sandwich principal on admission [11].

Blood samples from patients with ACS were taken at presentation and frozen at (-80) before analysis. Copeptin value was tested retrospectively.

The assay has an analytical detection limit of 0.4 pmol/l and a functional assay sensitivity (lowest value with an interassay $\text{CV} < 20\%$) < 1.0 pmol/l.

Establish the diagnosis: Follow up cardiac troponin I. Follow up ECG.

Statistical Analysis

Statistical analysis was done using the SPSS software package version 20.0.

Statistical analysis was done to obtain the mean, the standard deviation; the standard error of each mean and for comparison between the different groups involved in this study ONE WAY test was used for comparison between independent samples.

Results

The study population rolled 88 patients presenting to hospital by chest pain and admitted to coronary care unit (CCU) 30 patients had diagnosis of non ST elevated myocardial infarction (NSTEMI) (group 1) while 58 patients had diagnosis of unstable angina (UA) (group 2) who were assisted by copeptin level.

Baseline clinical characteristics

Age and sex

In our study, patients were 49 male patients (55.7%) while 39 patients (44.3%) were females. In group I: male patients were 19 patients (63.3%) while female patients were 11 patients (36.7%). In group 2: male patients were 30 patients (51.4%) while female patients were 28 patients (48.3%).

As regarding the age: In group 1 (NSTEMI) the mean age of patients was older than group 2 (UA) (60 ± 4 versus 53 ± 5 with p value < 0.001).

Risk factors for CAD

In our study as regarding smoking, the whole studied patients were 43 smokers (48,9%) and 45 were nonsmokers (51,1%). In group 1 (NSTEMI) 18 patients were smokers (60%) and 12 were nonsmokers (40%) and in group 2 (UA) 25 patients were smokers (43.1%) and 33 patients were nonsmokers (56,9%).

As regarding hypertension, the whole studied patients were 41 hypertensive (46.6%) and 47 were non hypertensives (53.4%). In group 1 (NSTEMI) 14 patients were smokers (46.7%) and 16 were non hypertensive (53.3%) and in group 2 (UA) 27 patients were hypertensive (46.6%) and 31 patients were non hypertensive (53.4%).

As regarding diabetes mellitus (DM), the whole studied patients were 44 diabetics (50%) and 44 were non diabetics (50%). In group 1 (NSTEMI) 17 patients were diabetics (56.7%) and 13 were non diabetics (43.3%) and in group 2 (UA) 27 patients were diabetics (46.6%) and 31 patients were non diabetics (53.4%).

As regarding blood cholesterol: In group 1 (NSTEMI) the mean cholesterol level of patients were higher than group 2 (UA) (245.20 ± 34.79 versus 152.60 ± 21.09 with p value < 0.0001).

As regarding blood triglycerides: In group 1 (NSTEMI) the mean triglycerides level of patients were higher than group 2 (UA) (185.6 ± 25.6 versus 142.60 ± 19.65 with p value < 0.01).

There are no significant differences as regarded smoking, hypertension and diabetes mellitus between two groups.

ECG changes

In our study we found, in group 1 (NSTEMI) 28 patients (93.3%) had ECG changes and only 2 patients had NSTEMI without ECG changes. And in group 2 (UA) 23 patients (39.7%) had ECG changes and 35 patients (60.3%) had normal ECG. There was significant difference between two groups as regarding presence of ECG changes with p value < 0.0001 .

In group 1 (NSTEMI): there were only 2 patient (7.1%) had hyper acute T wave, 4 patients (14.3%) had Q wave, 9 patients (32.1%) had inverted T wave, 8 patients (28.6%) with depressed ST segment and 5 patients (17.9%) with both depressed ST segment and inverted T wave.

While in group 2 (UA), none of patients had hyper acute T wave. there were 6 patients (26.1%) had Q wave, 12 patients (52.2%) had inverted T wave, 4 patients (17.4%) with depressed ST segment and only one patient (4.3%) with both depressed ST segment and inverted T wave.

We found significant higher percentage difference in patients with both ST segment depression and inverted T wave (17.9%) in group 1 (NSTEMI) as compared to (4.3%) in group 2(UA) with P value 0.022.

We found also significant difference in patients with Q wave (14.3%) in group 1 (NSTEMI) as compared to (26.1%) in group 2 (UA) with P value 0.032. and significant difference in patients with inverted T wave (32.1%) in group 1 (NSTEMI) as compared to (52.2%) in group 2 (UA) with P value 0.044.

As regarding hyper acute T wave and ST segment depression, there was no significance difference.

According to lab investigations

As regarding random blood glucose level. We classified patients in two groups. Group A (diabetic patients): RBS in group 1 (NSTEMI) was between 96 and 523 with mean 315 ± 89 and for group 2 (UA) was between 73 and 321 with mean 220 ± 77 . Group B (non diabetic): RBS in group 1 (NSTEM I) was between 80 and 212 with mean 114 ± 53 and for group 2 (UA) was between 77 and 162 with mean 119 ± 39 .

There are no significant differences as regarded random blood glucose level between two groups.

	Group I (n = 30)		Group II (n = 58)		Total (n = 88)	
	No.	%	No.	%	No.	%
Hyper acute T wave	2	7.1	0	0.0	2	3.9
$\chi^2(p)$	0.26					
Q wave	4	14.3	6	26.1	10	19.6
$\chi^2(p)$	0.032*					
Inverted T wave	9	32.1	12	52.2	21	41.1
$\chi^2(p)$	0.044*					
ST segment Depression	8	28.6	4	17.4	12	23.5
$\chi^2(p)$	0.089					
ST segment depression + inverted T wave	5	17.9	1	4.3	6	11.7
$\chi^2(p)$	0.022*					
Significant ECG changes						
Yes	28	93.3	23	39.7	51	58.0
No	2	6.7	35	60.3	37	42.0
$\chi^2(p)$	0.0001*					

Table 1: Comparison between the studied groups according to admission ECG changes.

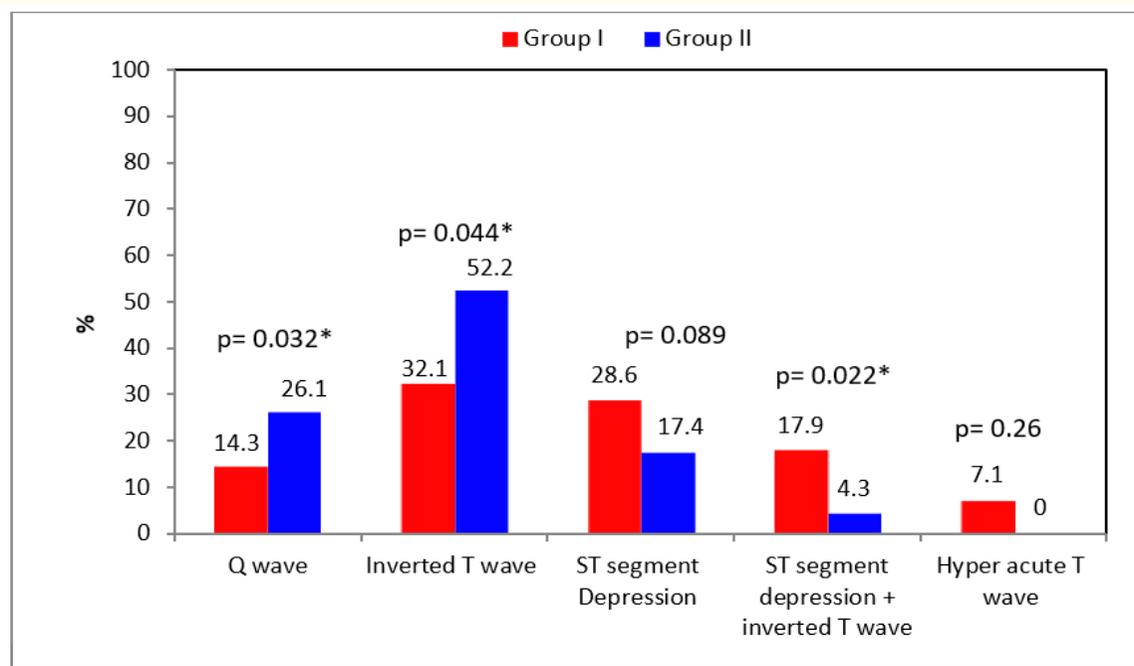


Figure 1: Comparison between the studied groups according to significant ECG changes.

According to cardiac markers and copeptin

In our study one of exclusion criteria was first cardiac markers were positive, so that both troponin and CK-MB were normal in 1st round.

In the 2nd round after 6 hours: CK-MB in group 1 (NSTEMI) were between 11.0 and 24.80 with mean 18.2 ± 4.7 while in group 2 (UA) were between 0.90 and 3.50 with mean 2.25 ± 0.78 . There was significant increase in CK-MB level in group I in 2nd round with p value < 0.0001.

While troponin in group 1 (NSTEMI) were between 0.73 and 4.81 with mean 2.98 ± 1.13 and in group 2 (UA) were between 0.001 and 0.3 with mean 0.22 ± 0.14 . There was also significant increase in troponin level in group I in 2nd round with p value < 0.0001.

We found in our study that all patients in group 1 had significant increase in both troponin and CK-MB levels while all patients in group 2 had no significant increase in troponin or CK-MB.

As regarding copeptin level on admission: in group 1 (NSTEMI) all patients had elevated copeptin level as the results were between 13.5 and 20 with mean 17.11 ± 1.89 .

But in group 2 (UA) there were only 10 patients had elevated copeptin level while the remaining 48 patients had copeptin level below 13.2 pmol/l as the results were between 6 and 16 with mean 8.39 ± 3.61 .

There was significant increase in copeptin level in group 1 (NSTEMI) in relation with group 2 (UA) with p value < 0.0001 table 2.

	Group I (n = 30)	Group II (n = 58)	Test of sig.
CK - MB 1st (ng/ml)			
Min. - Max.	1.0 - 3.40	0.90 - 3.50	t = 0.579 p = 0.449
Mean ± SD.	2.02 ± 0.68	2.14 ± 0.75	
Serum Troponin 1st (ng/ml)			
Min. - Max.	0.001 - 0.01	0.001 - 0.01	t = 0.054 p = 0.817
Mean ± SD.	0.0049 ± 0.0032	0.0051 ± 0.0028	
CK - MB 2nd (ng/ml)			
Min. - Max.	11.0 - 24.80	0.90 - 3.50	t = 84.30* p = 0.0001
Mean ± SD.	18.26 ± 4.71	2.25 ± 0.78	
Serum Troponin 2nd (ng/ml)			
Min. - Max.	0.73 - 4.81	0.001 - 0.3	t = 42.2* p = 0.0001
Mean ± SD.	2.98 ± 1.13	0.22 ± 0.14	
Significant increase in Cardiac markers			
Yes	30 (100.0)	0 (0.0)	$\chi^2 = 88.0^* p = 0.0001$
No	0 (0.0)	58 (100.0)	
Copeptin (pmol/l)			
Min. - Max.	13.5 - 20.0	6.0 - 16.0	t = 43.11* p = 0.0001
Mean ± SD.	17.11 ± 1.89	8.39 ± 3.61	

Table 2: Comparison between the two studied groups regarding markers.

Table 3 show the correlation between copeptin and other measured variables, it was found that there was a positive significant correlation between copeptin and random blood glucose level, CK-MB 2nd and serum Troponin 2nd measure while there was no significant correlation with other variables.

Copeptin	Pearson Correlation	p
Age	0.112	0.151
Random Blood Glucose	0.511**	0.001**
CK - MB 1 st	0.112	0.298
Serum Troponin 1 st	0.069	0.52
CK - MB 2 nd	0.638**	0.001**
Serum Troponin 2 nd	0.520**	0.001**
Cholesterol	0.141	0.262

Table 3: Correlation between copeptin and other measured variables.

Discussion

In this study, we are trying to determine the role of copeptin as an early marker for rapid rule out acute myocardial infarction in the studied population (involving unselected patients presenting to the emergency department with symptoms suggestive of acute myocardial infarction), bearing in mind that copeptin is not a cardiac enzyme (nonspecific) but is an indirect marker for arginine-vasopressin. Previous studies had detected that copeptin (the c-terminal part of the vasopressin prohormone) was increased in acute myocardial infarction [12,13].

Early release of copeptin in patients with MI

Copeptin level was measured for all patients included in our study within 4 hours from the onset of chest pain. The results of our study showed that copeptin level was significantly higher in patients with myocardial infarction as compared with patients with unstable angina. In other words, acute myocardial infarction was correctly excluded at admission from all patients with acute chest pain, using only one laboratory assessment in 48 out of 88 patients (54% of the entire studied group).

These data suggest that acute myocardial infarction induces a higher level of endogenous stress than unstable angina does, potentially related, at least in part of it, to the more prolonged course of chest pain in patients with acute myocardial infarction. Ischemia, as long as not accompanied by necrosis (i.e., unstable angina), does not seem to be a stronger trigger of copeptin release than are other causes of chest pain.

This result agrees with Khan SQ, *et al.* 2007 who studied copeptin as a novel and prognostic marker in acute myocardial infarction [14]. This study included 980 patients and reported that plasma copeptin was highest on admission in patients with diagnosis of myocardial infarction due to activation of the vasopressin system and reach plateau at day 3 to 5.

Till Keller, *et al.* 2010 found that copeptin improves early diagnosis of acute myocardial infarction. [12]. This study included 1,386 patients and detected that median copeptin level was highest in patients with acute myocardial infarction after 3 hours from the onset of chest pain. The study reported that, the determination of copeptin in addition to troponin levels improves diagnostic performance, especially early after chest pain onset.

Youlan L, *et al.* 2011 studied the comparison of the temporal release pattern of copeptin with conventional biomarkers in acute myocardial infarction [15]. This study included 145 patients undergoing successful primary percutaneous coronary intervention (PCI) for a first ST-elevation acute myocardial infarction presenting within 12 h of symptom onset. The study detected that copeptin level was already elevated on admission and peaked within the first hour after symptom onset and reported that copeptin has distinct release pattern in patients with acute myocardial infarction.

Maisel A, *et al.* 2013 found that copeptin helps in the early detection of patients with acute myocardial infarction [16]. This study included 1,967 patients and found an increase in copeptin level within the first 6 hours and reported that adding copeptin to cardiac troponin I allowed safe rule out of acute myocardial infarction with a negative predictive value > 99% in patients presenting with suspected acute coronary syndrome.

Zeinab H, *et al.* 2014 studied the impact of copeptin on diagnosis of acute coronary syndrome. This study included 45 patients (22 with acute myocardial infarction and 33 with unstable angina) and 33 apparently healthy persons. They found that patients with diagnosis with myocardial infarction had significantly higher level of copeptin in comparison to both other groups [17].

Sensitivity of copeptin

In our study we found that all patients with diagnosis of NSTEMI had elevated copeptin level with sensitivity of 100% when we used cutoff level 13.2 pmol/l and negative predictive value of 100%. In contrast with previous researches, we chose not to take 14 pmol/l as

a cutoff point, but to decrease the cutoff point to the degree that we can detect all patients with diagnosis of non ST elevated myocardial infarction, to be able in the future to detect the cutoff point at which we do not miss any patient with myocardial infarction coming to emergency department complaining of chest pain [18].

What is new in this study?

We concentrated on unstable angina and non ST elevation infarction, excluding raised ST infarction and frank infarction with raised Troponin in first hour to elucidate validity of Copeptin in only suspicious cases.

Study Limitations

1. This is a single-center study.
2. Thirty patients with NSTEMI is a small number for an MI rule out and confirmation by larger studies is wanted before copeptin can be adopted into clinical practice.
3. We cannot exactly detect the cost benefit associated with the more rapid exclusion of AMI provided by the additional use of copeptin.

Conclusion

Copeptin seems to be an ideal marker to rapid rule out of AMI. The additional use of copeptin may allow for a rapid and accurate rule out of AMI and might obviate the need for prolonged monitoring and serial blood sampling in the ED for the majority of patients. This fundamental change in clinical practice may provide the opportunity to significantly improve patient management in the ED.

Conflict of Interest

No conflict of interest.

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Role and Contributions of Authors

Samir Rafla: Rewriting the paper for submission.

Sahar Azab: The main investigator, co- head of the Thallium lab, work is her idea.

Mohamed Sadaka: Co supervisor.

Eman Soliman: Co supervisor, staff in Clinical Medicine department not cardiology department. Responsible about lab results and methodology.

Samy Soliman Fahim: This is his master thesis; he is the main investigator and writer of the thesis.

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