Role of Copeptin in Ruling out Acute Coronary Syndrome and Sizing of Infarction in National Heart Institute.

Elmarakby AM (MBBCH), Zahran ME (MD), Badran HA (MD), Onsy AM (MD)

Department of Cardiology, Faculty of Medicine, Ain shams University, Cairo, Egypt
d-marakby@hotmail.com

Abstract: Background: Acute coronary syndrome (ACS) is a very common health and economic burden in the world and accounts for more than 1 million of morbidities annually. Deaths due to ACS are nearly half of all deaths. Nearly 15–20 million patients each year admitted to the emergency room (ER) with typical chest pain, two-thirds of theme will be found not to have an ACS, so rule-in and exclusion seems to be very important. Biomarkers mainly troponins complement the clinical suspicion of ACS with the 12-lead ECG, but a major drawback its late release in the blood stream after ACS and thus the need for serial cardiac enzymes and prolonged monitoring for the final diagnosis or ruling out, the need for faster diagnosis and safe rule out of the patients with suspected ACS has led to the discovery of new biomarkers. Such a new biomarker is Copeptin which is nowadays well understood as an important marker of endogenous stress. **Aim and Objectives** is to investigate the effectiveness of using copeptinin safely ruling out NSTE-ACS very early after onset of symptoms and to asses if it has a prognostic value on determining the size of infarction or not. **Patients and Methods:** Any Patients presented to ER with symptoms suggesting ACS within maximum four hours of symptoms onset and don't have any of the exclusion criteria. **Results:** This study included 86 patients presented to the ED with symptoms suggestive for ACS mainly typical chest pain. The mean age for current study was 56.71±7.11 years ranged from 37-75 years. Most of our patients were males (71%), 45 patients (52.3%) were hypertensives, 41 patients (47.7%) were diabetics, 41 patients (47.7%) were smokers and 31 patients (36%) had a history of ischemic heart disease. All patients presented within 4 hours from symptoms onset with mean 2±0.71hours, 1st set of copeptin, troponin and CK MB withdrawn at time of admission, another set of troponin and CK MB withdrawn after 6 hours. 45 patients showed an elevated troponin with the 2nd set while only 1 patients had a troponin positive with the 1st set, copeptin was highly elevated in 43 out of those 45, sensitivity of copeptin in relation to troponin was 95.6%, while copeptin was high in 7% of the troponin negative group with a specificity 82.9%. The highly abnormal Copeptin showed a strong correlation with the peaked elevated CK MB 2nd set (r=0.701), but there were no statistically significant difference between copeptin positive and negative groups regarding risk factors, ECG changes, SWMAs or impaired EF% in echo. **Conclusion:** Copeptin is a novel biomarker that showed a great sensitivity towards NSTEACS and may improve the early and safe rule out of ACS in low to intermediate risk patients.

Keywords: Acute coronary syndrome; ST-elevation myocardial infarction; non-ST elevation myocardial infarction; Emergency Department; Early rule out; Copeptin; Biomarkers.

1. Introduction

Acute myocardial infarction (AMI) is a very common cause of death in the developed countries. While its prevalence in the developing countries is also steadily rising. Therefore, it is extremely important to ensure the early detection with a maximum diagnostic accuracy. These abilities will promote rapid interventions in AMI in the clinical setting and prevent the unsafe premature discharge of unrecognized AMI patients from the hospitals[1]. Initial evaluation of ACS depends on 12-lead electrocardiography recording and serial biomarker analysis, in complement to the clinical suspicion [2]. Cardiac troponin (cTn) T and I are considered the standard markers for myocardial cell injury and detection in blood stream is a part of the 4^{th}universal definition of myocardial infarction[3]. CTnT

assays lack sensitivity within the first hours of myocardial injury due to its delayed release, a phenomenon called 'troponin-blind period'. Serial blood sampling is therefore mandatory. There is growing interest in alternative new biomarkers which might be more early detectable after the myocardial injury[4]. Copeptin is a 39-amino acid-long peptide deriving from a pre-pro-hormone that consists of vasopressin, neurophysin II and copeptin[5]. It has been proved that copeptin rises every yearly after the onset of acute MI[6]. Copeptin is also a very strong biomarker for mortality and morbidity in patients with decompensated heart failure complicated after AMI[7].

Aim of the work:

The aim of the study is to investigate the effectiveness of using copeptin (a marker of

endogenous stress) in safely ruling out of NSTE-ACS and to asses if it has a prognostic value on determining the size of infarction or not.

2. Patients and Methods:

This is an observational study that included 86 patients who were admitted to the Emergency Department of National Heart Institute (NHI) complaining from symptoms suggestive for Acute Coronary Syndrome from 1st May 2018 to 1st Jan 2019, approval of the Ain shams university ethical committee was obtained according to the ethical guidelines of the 1975 declaration of Helsiniki as revised in 2008.

Inclusion criteria

Patients who presented with symptoms suggestive for Acute Coronary Syndrome mainly typical chest pain within a maximum four hours of onset of symptoms.

Exclusion criteria

1. Patients with onset of chest pain more than 4 hours.

2. STEMI.

3. End-stage renal disease which defined as GFR< 15 ml/min/1.73 m2 and/or patient on regular renal dialysis.

4. Anemia which defined as level of hemoglobin < 10 g/dl for men < 8 g/dl for women.

5. Hyponatremia (defined as level of Na+ < 125 mmol/l).

6. Major operation or major Injury in last month.

7. Cancer with life expectancy less than 6 months.

8. Pregnant women.

9. Age less than 18 years.

10. Lack of informed consent.

Patients who met the inclusion criteria were subjected to the following**:**

1) Proper History: Full history taking that Includes personal history with recording of age, gender, special habits like smoking, etc.), history of previous acute coronary syndrome (ACS) or similar attacks, history of cardiac interventions, history of co-morbidities like diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, ischemic heart disease, peripheral vascular disease,…etc.

2) Clinical examination: Full clinical examination including vital signs (ABP, Heart rate, respiratory rate…etc), assessment of the chest pain, general examination and cardiac examination for diagnosis and omit patient with exclusion criteria.

3) A 12-lead ECG: Obtained and read within 10 min of patient's arrival to the emergency department (ED). Serial ECGs at 15- to 30-min intervals during the first hour performed in symptomatic patients when initial ECG is non diagnostic.

4) Transthoracic echocardiography: Done for all patients within their admission stressing on the following data: LV ejection fraction (EF%), segmental wall motion abnormalities (SWMA), diastolic dysfunction and LV End diastolic and systolic diameters, ejection fraction measured using M-mode modality and considered abnormal below than 52%, measurement of left ventricular diameters is also obtained with 2-D echocardiography ranging from 4.2-5.9 cm for male and 3.9-5.3 cm for females for the normal diastolic diameters, and 22-58 ml for male, 19-49 ml for female for the normal systolic volumes.

5) Laboratory investigations: Routine laboratory parameters, including cbc, creatinine, urea, and NA were measured immediately after blood withdrawal by standardized methods. The MB fraction of creatine kinase measured by immunoassays with a reference value from 5 to 25 IU/L, value above 25 IU/L was described positive, Cardiac troponin cTnT was measured at admission time in all patients with the electrochemiluminescence immunoassay technology with detection limit of 0.01 ng/ml and measuring range of 0.01 to 25 ng/ml. Copeptin was measured in ethylenediaminetetraacetic acid plasma by sandwich immunoluminometric assay, the assay detection limit as described by themanufacturer was 0.4 ng/ml, the direct measuring range was 0.4 ng/ml to 100ng/ml, A value above 0.4ng/ml was considered positive, 2nd set for CK-MB and Troponin cTnT withdrawn after 6 hours from admission.

3. Results

This an observational Study was conducted on 86 patients presented with symptoms suggestive for ACS within four hours from the onset of symptoms at National Heart Institute.

Table 1: Basic demographic data, risk factors and laboratory data of the studied cases

		No. = 86
Gender	Female	25 (29.1%)
	Male	61 (70.9%)
Age	Mean ± SD	56.71 ± 8.61
	Range	37 – 77
Smoker	Non smoker	45 (52.3%)
	Smoker	41 (47.7%)
DM	Non diabetic	45 (52.3%)
	Diabetic	41 (47.7%)

		No. = 86
HTN	Not hypertensive	41 (47.7%)
	Hypertensive	45 (52.3%)
IHD	Negative	55 (64.0%)
	Positive	31 (36.0%)
Hb	Mean ± SD	12.37 ± 1.35
	Range	10.5 – 16
Cr	Mean ± SD	1.11 ± 0.28
	Range	0.6 – 1.8
Urea	Mean ± SD	44.02 ± 10.11
	Range	25 – 66

The previous table shows that: 61 (71%) patients were males while female were 25 (29%), age ranged from 37 to 77 with mean age 56±8 years, 45 patients (52.3%) were hypertensives, 41 patients (47.7%) were diabetics, 41 patients (47.7%) were smokers and 31 patients (36%) have a history of ischemic heart disease

Clinical Data:

Patients were categorized into two groups according to the final results of Cardiac troponin cTnT:

Table 2: Comparison between Troponin positive and Troponin negative groups regarding ECG, onset of chest pain and echo findings

		Troponin negative No. = 41	Troponin positive No. = 45	Test value	P-value	Sig.
ECG changes suggestive for ischemia	Normal	**15 (36.6%)**	**8 (17.8%)**	3.873*	0.049	S
	Abnormal	**26 (63.4%)**	**37 (82.2%)**			
Onset of chest pain/ hours	Mean ± SD	2.20 ± 0.75	1.87 ± 0.76	2.020•	0.047	S
	Range	1 – 4	1 – 3			
Diastolic dysfunction	Grade I	23 (56.1%)	19 (42.2%)	4.586*	0.101	NS
	Grade II	16 (39.0%)	26 (57.8%)			
	Grade III	2 (4.9%)	0 (0.0%)			
LV Ejection Fraction %	Mean ± SD	53.66 ± 7.29	50.49 ± 8.51	1.846•	0.068	NS
	Range	35 – 72	34 – 64			
	Good	14 (34.1%)	14 (31.1%)	0.090*	0.764	NS
	Impaired	27 (65.9%)	31 (68.9%)			
LV end diastolic diameter (cm)	Mean ± SD	53.27 ± 6.78	56.00 ± 8.17	-1.679•	0.097	NS
	Range	39 – 70	39 – 70			
LV end systolic volume (ml)	Mean ± SD	39.66 ± 7.65	43.42 ± 9.24	-2.046•	0.044	S
	Range	28 – 62	28 – 62			
SWMA	**Absent**	**22 (53.7%)**	**13 (28.9%)**	**5.454***	**0.020**	**S**
	Present	**19 (46.3%)**	**32 (71.9%)**			

Table 3: Comparison between Troponin positive and negative groups regarding biomarkers:

		Troponin negative No. = 41	Troponin positive No. = 45	Test value	P-value	Sig.
Troponin 1st (ng/ml)	Negative	41 (100.0%)	44 (97.8%)	0.922*	0.337	NS
	Positive	0 (0.0%)	1 (2.2%)			
Troponin 2nd Set (ng/ml)	Negative	41 (100.0%)	0 (0.0%)	86.000*	0.000	HS
	Positive	0 (0.0%)	45 (100.0%)			
CK MB 1st (IU/L)	Median (IQR)	18 (15 – 23)	18 (16 – 22)	-0.009	0.993	NS
	Range	11 – 45	12 – 28			
CK MB 1st (IU/L)	Normal	33 (80.5%)	40 (88.9%)	1.180	0.277	NS
	Abnormal	8 (19.5%)	5 (11.1%)			
Ck MB 2nd (IU/L)	Median (IQR)	22 (18 – 23)	88 (66 – 128)	-7.353	0.000	HS
	Range	12 – 200	25 – 346			
Ck MB 2nd (IU/L)	**Normal**	**32 (78.0%)**	**5 (11.1%)**	**39.214**	**0.000**	**HS**
	Abnormal	**9 (22.0%)**	**40 (88.9%)**			
Copeptin (ng/ml)	Median (IQR)	**0.37 (0.31 – 0.4)**	**3.08 (2.59 – 4.58)**	-7.321	**0.000**	**HS**
	Range	0.13 – 2.56	0.11 – 7.84			
Copeptin (ng/ml) at admission time T0	**Normal**	**34 (82.9%)**	**2 (4.4%)**	**54.296**	**0.000**	**HS**
	Abnormal	**7 (17.1%)**	**43 (95.6%)**			

In the previous table: Copeptin was elevated in 43 out of 45 patients (95.6%) of the finally diagnosed troponin positive group, while the 1st set of CK MB and Troponin were not detectable. Troponin appeared positive in only 1 patient during the 1st set, while CK MB was positive in only 5 patient with its 1st set. Copeptin elevated also in 7 patients (17.1%) whom are finally diagnosed as troponin negative (Figure 1). CK MB 2nd set was elevated in 89% of the troponin positive group.
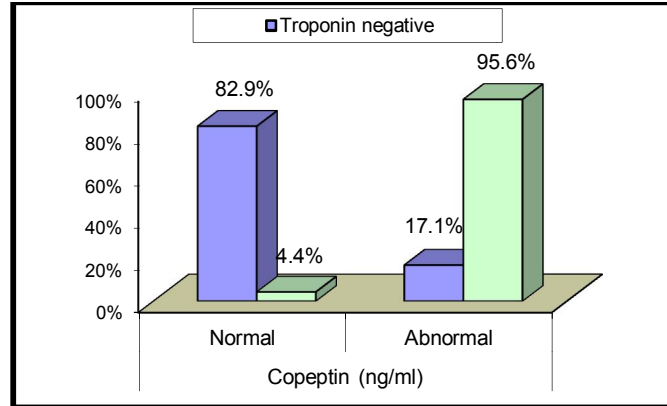
Figure 1: Comparison between Troponin positive and troponin negative groups regarding copeptin

Table 4: Diagnostic accuracy of troponin 2nd set, CKMB 2nd set and copeptin level in prediction of NSTE-ACS cases

	End diagnosis (Troponin Positive group, 45 no patients suspecting NSTE-ACS)				
	Sensitivity	Specificity	PPV	NPV	Accuracy
Ck MB 2nd set (IU/L)	88.9%	78.0%	81.6%	86.5%	0.837
Copeptin (ng/ml) On admission T0	**95.6%**	**82.9%**	**86.0%**	**94.44%**	**0.895**

As shown in Table 4: Copeptin appeared to be detectable in its 1st and only set at time of admission in 95.6 % of the finally elevated troponin patients that detected during the 2nd set troponin after 6 hours,

Copeptin's specificity was comparable to CK MB, 83 % for copeptin, 78 % for CK MB. The NPV of Copeptin was 94.5 % while it was 86.5 for CK MB 2nd set.

Table 5: Comparison between abnormal Copeptin and normal Copeptin group regarding onset of chest pain, ECG and Echo findings

		Copeptin (ng/ml)		Test value	P-value	Sig.
		Normal	Abnormal			
		No. = 36	No. = 50			
ECG changes suggestive for ischemia	Normal	11 (30.6%)	12 (24.0%)	0.459*	0.498	NS
	Abnormal	**25 (69.4%)**	**38 (76.0%)**			
Onset of chest pain/ hours	Mean ± SD	2.11 ± 0.75	1.96 ± 0.78	0.901•	0.370	NS
	Range	1 – 4	1 – 3			
Diastolic dysfunction	Grade I	18 (50.0%)	24 (48.0%)	3.040*	0.219	NS
	Grade II	16 (44.4%)	26 (52.0%)			
	Grade III	2 (5.6%)	0 (0.0%)			
LV Ejection Fraction %	Mean ± SD	53.75 ± 7.35	50.74 ± 8.39	1.728•	0.088	NS
	Range	35 – 72	34 – 64			
	Good	14 (38.9%)	14 (28.0%)	1.130*	0.288	NS
	Impaired	**22 (61.1%)**	**36 (72.0%)**			
LV end diastolic diameter (cm)	Mean ± SD	53.58 ± 6.26	55.50 ± 8.43	-1.153•	0.252	NS
	Range	43 – 70	39 – 70			
LV end systolic volume (ml)	Mean ± SD	39.97 ± 7.54	42.82 ± 9.30	-1.513•	0.134	NS
	Range	29 – 62	28 – 62			
SWMA	Absent	17 (47.2%)	18 (36.0%)	1.092	0.296	NS
	Present	**19 (52.8%)**	**32 (64.0%)**			
1-ECG changes suggestive for ischemia: 76% of the patients in copeptin positive group hadan ECG changes compared to 69% in the negative group. 2-Impaired EF%: 36% of the patients in the positive group showed an impaired EF% 1- assessed by TTE compared to 22% in the negative group. 3-SWMAs assessed by TTE: 64% of the patients in the positive group had a SWMAs by TTE compared to 53% in the negative group as seen in table 5.						

4. Discussion:

The early differential diagnosis of acute chest pain is a major challenge in the ER. it is mandatory to correctly identify those patients with AMI from whom who haven't, as the vast majority of patients presenting with the symptoms suggestive of ACS will not have

AMI at the end (8). Available tools are effective but time consuming. It is recommended to measure cardiac troponin which is the gold standard marker for myocardial damage, in a serial blood samples (9). A major drawback of these traditional markers is their inability to be detectable in blood early after the myocardial since these cardiac biomarkers starts to rise after 4-6 hours from the onset of myocardial cell injury reaching the peak within 12-24 hours (10).

In CHOPIN (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction) one of the largest multicenter studies conducted on 1967 patients presented to the ED with typical chest pain, it found that only 8% had a final diagnosis of AMI (STEMI and NSTEMI) whereas >60% had a non-cardiac origin of their symptoms (11).

Our study found that copeptin levels was high >0.4ng/ml in 50 out of 86 patients, 45 patients out of those 50 patients were found to have an elevated cTnT during the 2nd set and that was consistent with the 1st study investigated the response of circulating copeptin levels after acute myocardial infarction in Leicester Acute Myocardial Infarction Peptide (LAMP) Study by (Khan et al.,2007).

In our study copeptin level shows a great sensitivity towards the suspected NSTE-ACS patients reached 95.6% with a specificity 82.8% and a high NPV 94.4% and that was consistent with the results delivered from (Youlan L. Gu et al., 2011) that studied the unique release pattern of copeptin in blood after AMI in relation to the conventional cardiac biomarkers, this study found that copeptin had a 85% sensitivity if patient presented within 3 hours of onset of chest pain while if the patient presented within 1 hour of onset of chest pain the sensitivity was 100%.

Our study confirms and extends the findings of recent previous studies, which reported that copeptin levels in AMI patients were maximal on admission in contrast to cTnT (Keller T et al., 2010), In our study we found that Copeptin was abnormally high (>0.4 ng/ml) in 43 out of 86 patients at the time of admission while the gold standard biomarker troponin T was still undetectable during the 1st set except for just 2 patients and that was completely consistent with (T Reichlin et al., 2009) who found that Copeptin levels at admission were highest in the group of patients presenting 0 to 4 h after onset of symptoms while Troponin T levels were lowest in patients presenting earliest and rising with increasing time since onset of symptoms.

We proved in our study that copeptin released in the blood stream several minutes after onset of chest pain, and that appeared in 43 (95.6%) out of 45 the finally detected troponin positive patients with the 2nd set, 16 patients out of those 43 was within the 1st hour of chest pain while the remaining 27 patinets was within the next 3 hours of symptoms, and that was also

proved with another multicenter study on 1967 patients presenting to the ED within 6 hours of chest pain onset by (Alan Maisel et al., 2013) finding that AMIs that are not detected by the initial cTnI alone were picked up with copeptin in 23 (72%) of 32 patients while NSTEMI undetected by cTnI at 0 h were detected with copeptin in 10 (53%) of 19 patients.

In our study we didn't have a permission to discharge patients with initially copeptin and troponin negative value as we are an observational study but regarding this point a recent study by (Martin Mockel et al., 2015) investigated this part, that study was conducted on 902 low-risk patients with suspected ACS were randomly assigned to either serial cTnT testing as recommended 1st and 2nd set or single troponin and copeptin level at time of admission only. In the experimental arm, if both troponin and copeptin was negative, the patient was eligible for discharge without the need for serial cTnT testing, then a 30 days close follow up for both group regarding the primary safety end points that was all cause death, survived sudden cardiac death, acute myocardial infarction, acute life threatening arrhythmia or readmission with ACS, and the results was that a similar event rate in both study arms recommending that the combined cTnT / copeptin strategy is as safe as the standard procedure.

The potential advantage of the safe and early rule out of low risk patients who presented with typical chest pain would result in decreasing the length of hospital stay and ED overcrowding from 7hours to 4 hours as stated by (Martin Mockel et al., 2015), and from 3.0 hours to 1.8 hours as mentioned by (Alan Maisel et al., 2013).

In our study we tried to figure out if there is a correlation between the abonrmally high copeptin level (>.4 ng/l) and the sizing of infarcted area detected by extremely elevated CK MB and detection of a newly impaired EF % in echo or a new SWMAs. We found that there is a significant positive correlation between Copeptin level and CK MB 2nd set (r = 0.701 with p-value < 0.01), that was consistent with (M.O. AY et al., 2017) that stated that there is a positive correlation between rising copeptin level and CK MB mass (r=0.246 with p vlue <.002), but there was no significant correlation between abnormally elevated Copeptin level >0.4 ng/l and a recently impaired EF% or recent SWMAs in Echo, but A recent study by (Asthildur A et al., 2018) mentioned that there is no correlation between Copeptin/troponin and area at risk (AAR), final infarct size (FIS) nor myocardial salvage index (MSI) defined by Cardiac MRI.

Conclusion

Copeptin seems to be an ideal partner for cardiac troponins for the rapid rule out of AMI. The

combination of copeptin and troponin significantly improved the diagnostic accuracy for AMI at presentation as compared to troponin alone. Consequently, 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 and to reduce treatment cost.

Recommendations

- We recommended to do study on large number of patients.
- Mid and Long term complications must be included in the other study.
- Value of Copeptin in the prognosis of Acute Myocardial Infarction can be assessed in other studies.
- Further specific imaging modalities should be used with copeptin for the definite diagnosis of AMI like MDCT or CMR.
- Copeptin level should be assesed in a serial manner during the 1st day of presentation to ED to reach a definite cut off point and identify the maximum peak of its elevation.

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