

N-Terminal PRO-BNP in Acute Coronary Syndrome Patients with ST Elevation Versus Non ST Elevation in Qassim Region of Saudi Arabia

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Abstract:

Aim: To investigate the differences in the secretion of N-terminal pro B-type natriuretic peptide (NT-pro BNP) and conventional cardiac markers in patients with STE-ACS vs. NSTEMI-ACS as a trial to solve the dilemma of the early detection of myocardial ischemia in NSTEMI-ACS.

Design: Case control hospital based study.

Setting: King Fahad Specialist Hospital, Buraidah, Kingdom of Saudi Arabia.

Patients and methods: Sixty two patients with acute coronary syndrome (ACS) were divided into 2 groups according to ECG: group1 with elevated ST segment in ECG (STE-ACS) and group 2 with non elevated ST segment (NSTEMI-ACS). Twenty healthy subjects with matched age and sex were enrolled as control group in this study. In the sera of all subjects, levels of NT –proBNP, creatine kinase (CK)-MB isozyme and troponin T (Tn-T), were measured by different kits.

Results: CK-MB and Tn-T were both significantly higher in STE-ACS patients as compared to NSTEMI-ACS patients. Conversely, NT-proBNP was significantly higher in NSTEMI-ACS patients than STE-ACS especially within 4 hours from onset of chest pain. This suggested a larger ischemic insult despite the smaller extent of myocardial necrosis compared with STE-ACS patients. Comparison between sensitivity and specificity of NT-proBNP, Tn-T and CK-MB levels by ROC curves revealed marked difference of area under the curves with higher sensitivity and specificity of NT-proBNP in NSTEMI-ACS patients.

Conclusions: NT-proBNP can serve as a sensitive marker in the early phase of NSTEMI-ACS patients as compared to conventional markers of myocardial damage.

Subject category: Clinical Biochemistry

Keywords: Myocardial ischemia, non elevated ST segment, NT-proBNP, CK-MB, TnT.

Running title: BNP in acute coronary syndrome

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Introduction

The elevated serum level of NT-proBNP in patients with left ventricular (LV) dysfunction has shown a close correlation with the BNP level. Many reports have shown that the absolute increment of NT-proBNP exceeded that of BNP, and that NT-proBNP can be a more discerning marker for the detection and evaluation of cardiac dysfunction than BNP. ⁽¹⁾ B-type natriuretic peptide (BNP) also, called brain natriuretic peptide, and NT-proBNP can help to identify and accurately discriminate CHF from respiratory disease causes of dyspnea. ⁽²⁻³⁾ NT-proBNP measurements act as a guide to current treatment strategies, as well as novel strategies, in patients with acute myocardial infarction and as markers for the severity of heart failure. ^(4; 5) NT-proBNP provides information that may be superior to clinical judgment for the diagnostic evaluation of the patient with possible HF. It is a surrogate biomarker for prognosis after STEMI that is closely associated with myocardial damage as assessed by contrast-enhanced Cardiac MRI. ⁽⁶⁾ It is also an independent predictor of survival in patients with hypertension and increased left ventricular mass. ⁽⁷⁾ CK-MB acts as a marker of cytosolic damage that reflects the area at risk and the resultant size of the infarction. Whereas Tn-T acts as a marker of myofibril damage and elevated in proportion to infarct size per se. The clinical spectrum of ACS consists of ST elevation (STE) myocardial infarction (MI) (STEMI) and non-ST elevation (NSTEMI) or unstable angina (UA), which are classified from the acute phase electrocardiography (ECG) changes and the development of myocardial necrosis. STEMI caused by acute total coronary occlusion, whereas NSTEMI is associated with vulnerable plaque and subocclusive thrombosis. ⁽⁸⁾ Hence, we evaluate the clinical utility and early detection of myocardial ischemia is elevated in NSTEMI-ACS and the best time for treatment of disease by synthetic peptide molecule.

Subjects and Methods

It is a case control hospital based study in which 62 selected patients with acute chest pain or dyspnea were included. The patients were diagnosed as ACS according to Braunwald's classification, ⁽⁹⁾ or acute MI (AMI)

according to the redefined ESC/ACC Committee criteria were admitted to Coronary

Care Unit (CCU), King Fahad Specialist Hospital. Fifty four of them were men and 8 were females with ages in the range of 21-65 years. All patients presented to CCU within 10 hours from the onset of chest pain. Twenty age and sex matched healthy subjects served as the control group. The patients had cardiopulmonary resuscitation before admission, serum creatinine level >2.0 mg/dl or overt pump failure (\geq NYHA class II) were excluded in order to focus on the effect of myocardial ischemia per se on the release of NT-pro-BNP. All patients were subjected to standard 12-lead ECG immediately after admission and were classified into STE and NSTEMI groups. Patients with ST segment elevation at the J point in 2 or more consecutive leads (with the cut-off point being >0.2 mV in leads V1, V2, or V3, and >0.1 mV in the other leads) were defined as having STE-ACS while patients with ST segment depression, T wave inversion, or no ECG abnormalities were defined as having NSTEMI-ACS. Transthoracic 2-dimensional echocardiography was performed within 24 h of admission. The LV end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured according to the guidelines of the American Society of Echocardiography. ⁽¹⁰⁾ The LV ejection fraction (LVEF) was calculated by the modified Simpson's method. The study had formal approval of the ethical committee of Kingdom of Saudi Arabia, Ministry of Health.

Blood samples were drawn from every patient immediately after admission, centrifuged for 20 min at 2000xg at 4°C, and sera were separated divided into aliquots, kept at -70°C for biochemical measurements of cardiac markers. NT-proBNP was measured by using sandwich enzyme immunoassay kit for the quantitative determination of human N-terminal proBNP human in serum from Alpco diagnostics™ USA. Catalog # (SK-1204 BNP fragment EIA). Serum level of Tn-T was determined by chemiluminescent immunoassay system (Immulite) using available kit (Diagnostic Products Corporation U.S.A). Serum CK-MB levels were measured kinetically by UV method.

Statistical Analyses

SPSS version 16 was used in analysis of the data. The cardiac markers were expressed as mean \pm standard errors. The NSTEMI-ACS

and STE-ACS groups were compared by the Mann-Whitney U test. ANOVA tests were used to compare between different cardiac markers. Correlation coefficients were calculated to assess the relation between NT-proBNP and CK-MB, TnT. ROC curves were done and area under the curves were determined to compare the sensitivity and specificity of different cardiac markers in STE-ACS and NSTEMI-ACS. The cardiac markers and NT-proBNP levels on admission were grouped according to the time from onset of chest pain to admission of hospital, after which the NSTEMI-ACS and STE-ACS values in the patients were compared by using independent T- test at cut point 4, 6 and 8 hours to detect the maximum secretion of

NT-proBNP. A p-value less than 0.05 were considered statistically significant.

Results

The data of the patients with acute coronary syndrome (ACS) were shown in table 1. The total number of STE-ACS was 36 whereas the number of NSTEMI-ACS was 26 patients. There were no significant differences in age, DM, previous MI and hyperlipidemia between STE-ACS and NSTEMI-ACS. However, the females were mainly affected by STE-ACS. Smoking also was significantly increased in STE-ACS. There was no significant difference in EF% or angiography between 2 groups.

Table 1: Baseline characteristics of the patients with acute coronary syndrome (ACS)

	STE-ACS (n=36)	NSTEMI-ACS (n=26)
Age , years	60.72± 0.9	62.38 ± 0.8
Male /female	28 / 8	26 / 0
Smoking n (%)	20 (55.5%)	10 (38%)
DM, n (%)	20 (55.5%)	12 (46.1%)
Hyperlipidemia, n (%)	28 (77.7%)	18 (69.2%)
Previous MI, n (%)	12 (33.3%)	12 (46.15)
EF%	(57.1±9.8%)	(56.6±10.9%)
Coronary angiography:		
One vessels disease	24 (66.7%)	16 (61.5%)
Two vessels disease	8 (22.2%)	8 (30.7%)
Three vessels disease	4 (11.1%)	2 (7.8%)

STE-ACS, ST elevation acute coronary syndrome; NSTEMI-ACS, non-ST elevation acute coronary syndrome; EF%, ejection fraction; MI, myocardial infarction.

Unlike the conventional markers, the NT-pro-BNP level on admission was significantly higher in the NSTEMI-ACS compared to STEMI-ACS as shown in figure 1. The conventional

cardiac markers (Tn-T and CK-MB) levels on admission were significantly higher in STEMI-ACS patients than NSTEMI-ACS as shown in figures 2, 3 respectively, and table 2.

Table 2: Comparison of cardiac markers in all patients with ACS

	Mean \pm SE	P	Minimum	Maximum	percentiles		
					25th	50 th (median)	75th
NT-proBNP (pg/ml)	1124.35 \pm 103.9	0.01	200	2800	380	680	2000
Tn-T (ng/ml)	0.41 \pm 0.02	0.002	0.01	0.80	0.32	0.45	0.6
CK-MB (IU/L)	10.75 \pm 0.6	0.000	5.60	19.20	6.1	9.2	15

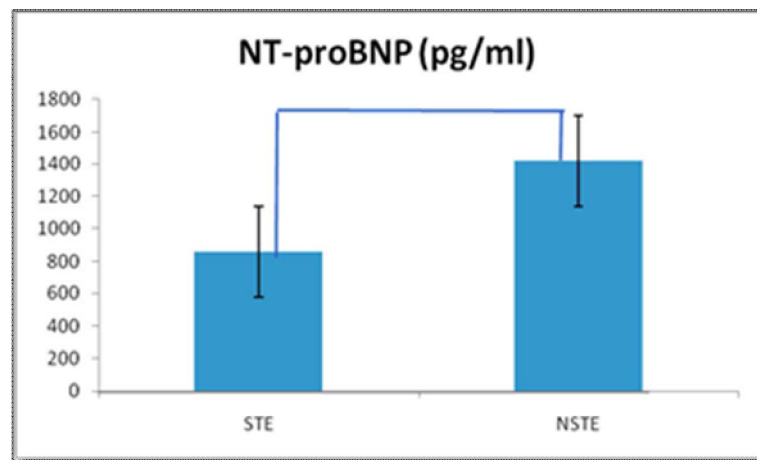


Figure 1: NT-proBNP in STE-ACS and NST-ACS

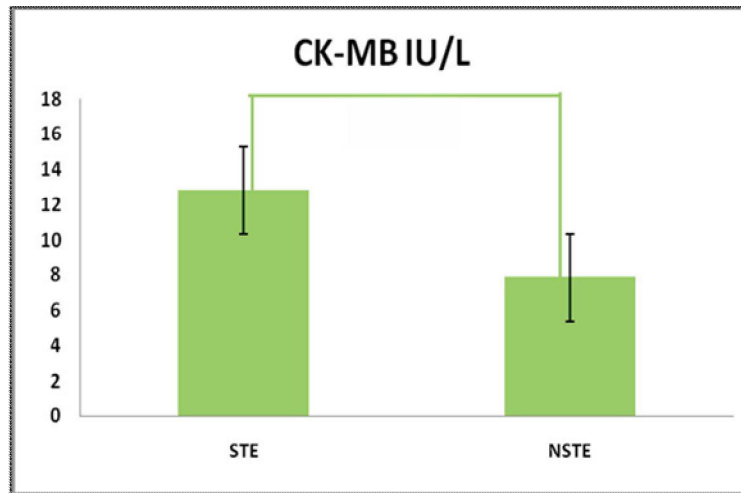


Figure 2: CK-MB in STE-ACS and NST-ACS

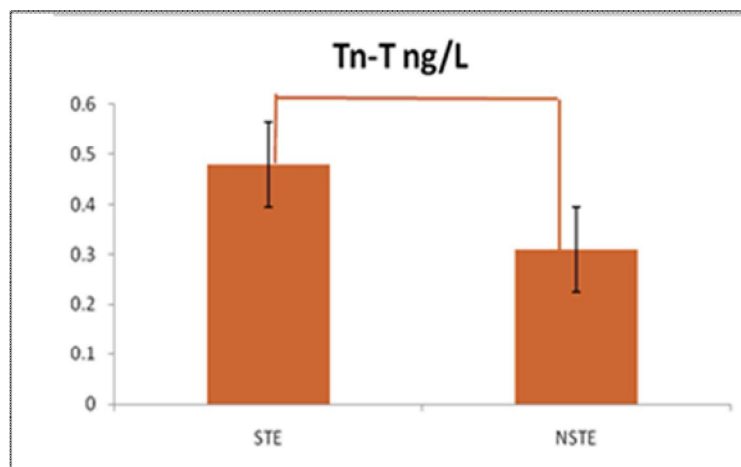


Figure 3: Tn-T in STE-ACS and NST-ACS

To determine the sensitivity and specificity of these 3 cardiac markers, ROC (Relative Operating Characteristics) curves were done. ROC curves of NSTE-ACS patients showed that NT-proBNP had higher sensitivity and specificity, followed by Tn-T then CK-MB. The area under the curves were 0.68, 0.31, 0.17, respectively, (figure 4). On the other hand, ROC curves of STE-ACS patients showed that CK-MB had higher sensitivity and specificity, followed by Tn-T then NT-proBNP. The area under the curves were 0.829, 0.690, 0.321, respectively, (figure 5). There was a positive correlation between Tn-T and CK-MB ($r = 0.3$,

$p = 0.01$) and inverse correlation between NT-proBNP and CK-MB ($r = -0.2$, $p = 0.03$). There was no significant difference in the LVEF determined by echocardiography between NSTE - ACS patients ($57.1 \pm 9.8\%$) and STE-ACS patients ($56.6 \pm 10.9\%$) because the patients with pump failure (\geq Killip class II) were excluded in this study. NT-proBNP increased in NSTE-ACS patients in the early phase of ACS and it was inversely proportional to the duration of chest pain. The increase was more profound when the duration of chest pain was ≤ 4 hours than ≤ 6 or ≤ 8 hours as shown figures in 6,7 and 8 respectively.

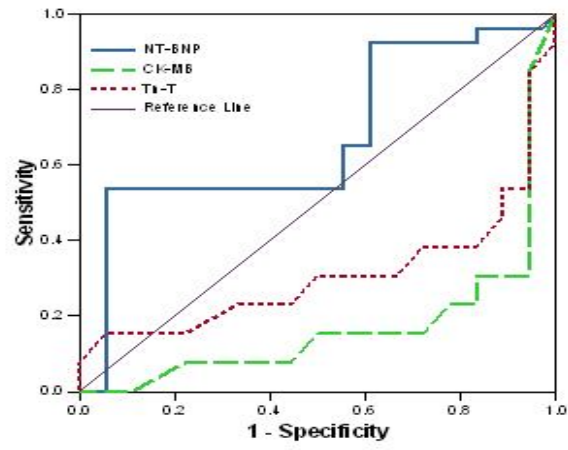


Figure 4: ROC Curve in NSTEMI-ACS

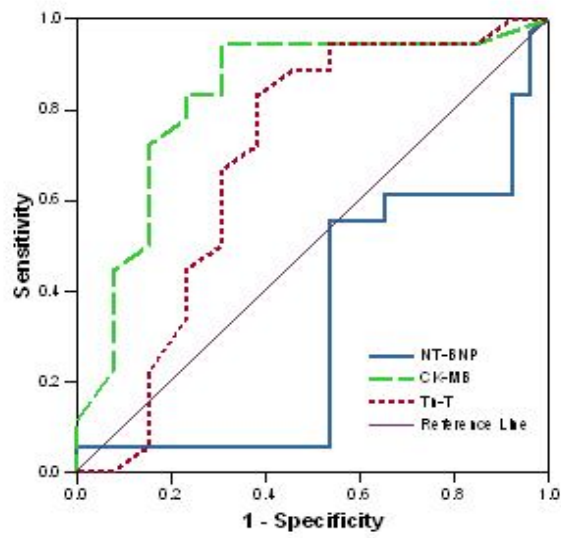


Figure 5: ROC Curve in STEMI-ACS

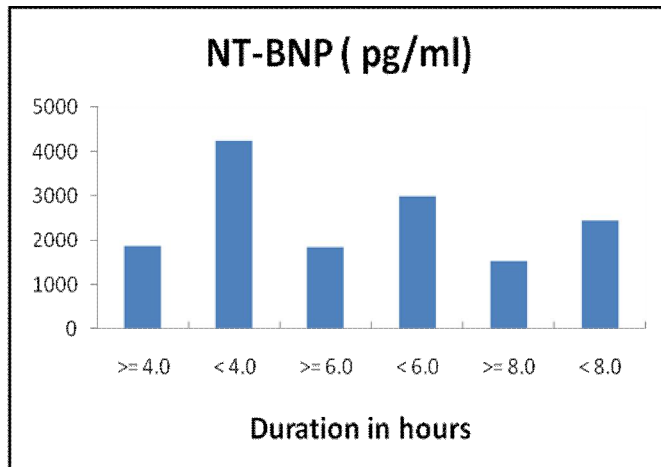


Figure 6: NT-proBNP in all patients with ACS

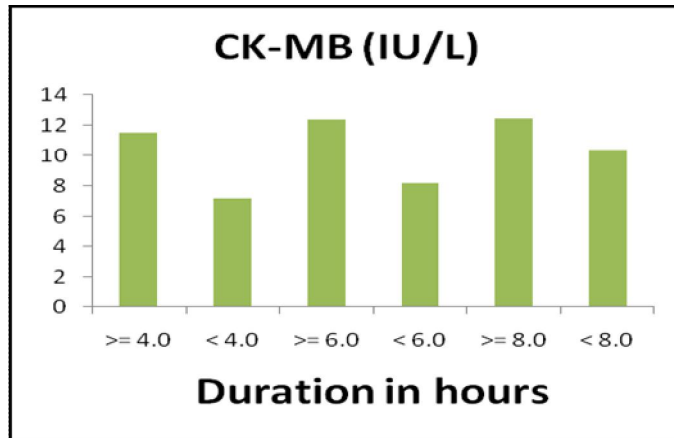


Figure 7: CK-MB in in all patients with ACS

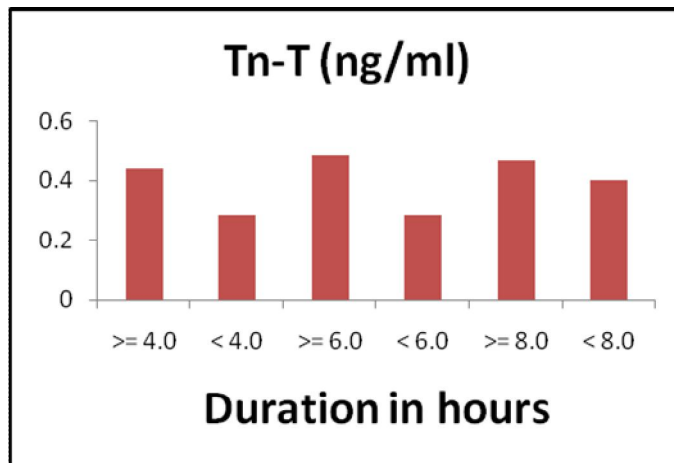


Figure 8: Tn-T in all patients with ACS

Discussion

Cardiac markers, such as troponin T (Tn-T), and creatine kinase (CK)-MB isozyme, detect the development of minor myocardial necrosis, and have emerged as powerful predictors of risk in patients with ACS.^(11; 12) Pro-BNP is synthesized as a pro-hormone by cardiac myocytes and then is cleaved by enzyme to N-terminal proBNP (NT-proBNP) and BNP. NT-proBNP levels predicted long term survival in patients. The patients where NT pro-BNP quartile was twice are likely to die as compared to patients with left ventricular hypertrophy in the lowest NT-proBNP quartile.⁽⁷⁾

In this study, Nt-proBNP was significantly higher in NSTEMI-ACS patients than in STEMI-ACS patients. This was despite lower values of the conventional cardiac markers CK-MB and Tn-T in NSTEMI-ACS patients. The increment of NT-proBNP in NSTEMI-ACS patients was inversely proportional to the duration of chest pain. This increase was more profound when the duration of chest pain was ≤ 4 hours than ≤ 6 or ≤ 8 hours. It increased during the hyperacute phase in NSTEMI-ACS patients, and didn't raise by the process of myocardial necrosis but the ischemic insult per se. This may be explained on the basis that the release kinetics of cardiac markers, especially as NT-proBNP, in patients with NSTEMI-ACS differed from that in the STEMI-ACS patients. The ischemic area or area at risk showed different spectrum in these 2 groups. The massive elevations of NT-pro-BNP observed in the early phase of coronary syndrome seemed to be independent of ventricular performance. Moreover, STEMI was caused by acute total coronary occlusion, whereas NSTEMI was associated with vulnerable plaque and subocclusive thrombosis.⁽⁸⁾ The myocardial ischemia was also a stimulus for the release of BNP and NT-proBNP.^(13;14) The underlying pathomechanism was not fully understood, but a direct release of BNP from ischemic cardiomyocytes in addition to ischemia induced by increase in ventricular wall stress was postulated. Moreover, there is an evidence suggestive of a protective role of BNP on the myocardium. BNP and other natriuretic peptides limit the extent of tissue infarction during ischemia and reperfusion. The mechanism of cytoprotection is related to cGMP accumulation and opening of ATP-sensitive K (+) channels.^(15;16) The early activation of the natriuretic peptide receptor/cGMP signaling system may be

an important autocrine / paracrine response in cardiac ischemia. This includes inotropic effects, acute regulation of coronary vascular tone and attenuation of the susceptibility of myocardium to ischemic injury, suppression of growth and proliferative responses in a variety of myocardial and vascular cells. In ischemic myocardium, acute treatment with BNP prior to and during coronary artery occlusion exerts a markedly protective, concentration-dependent infarct-limiting action. This cytoprotective effect of the natriuretic peptide signaling pathway might conceivably represent an alternative endogenous salvage pathway in myocardium which is potentially exploitable therapeutically. Taken together, the acute actions of natriuretic peptides on the coronary vasculature and in myocardial ischemia suggest a profile of activity that may be therapeutically beneficial in the management of patients with acute coronary syndromes.⁽¹⁷⁾ Age stratification of NT-proBNP using cut points of 450, 900, and 1,800 ng/L (for age groups of <50, 50-75, and >75 years) reduced false-negative findings in younger patients, reduced false-positive findings in older patients, and improved the overall positive predictive value of the marker without a change in overall sensitivity or specificity.⁽¹⁸⁾ In this study, the elevation of NT-proBNP was much higher in the NSTEMI-ACS patients than STEMI-ACS patients ($p=0.01$). This in agreement with another study, NT-proBNP was higher in NSTEMI-ACS patients than STEMI-ACS patients. Such early increase would reflect the amount of ischemic insult to the myocardium rather than the actual extent of myocardial damage or degree of heart failure.⁽¹⁹⁾ A correlation between LVEF and plasma levels of BNP ($r = -0.44$, $p=0.002$) was detected.⁽⁶⁾ However, in this study, this correlation couldn't be observed because heart failure was excluded. The use of NT-proBNP for the evaluation of the patient with suspected acute HF is useful, cost-effective, and may reduce adverse outcomes compared with standard clinical evaluation without natriuretic peptide testing.⁽²⁰⁾

In a multivariate Cox regression model, N-BNP added prognostic information above and beyond Killip class, patient age, and left ventricular ejection fraction. In patients with no evidence of clinical heart failure, N-BNP remained a significant predictor of mortality after adjustment for age and ejection fraction. N-BNP

is a powerful indicator of long-term mortality in patients with ACS and provided prognostic information above and beyond conventional risk markers.^(21; 22)

Conclusion

NT-proBNP can be serve as an early sensitive marker of ACS than other traditional cardiac markers (CK-MB and Tn-T) as it is increased significantly in the early phase of ACS when the chest pain duration is less than 4 hours. It is sensitive and specific than other traditional cardiac markers in the early diagnosis of NSTEMI-ACS which caused very big problem in the early diagnosis than STEMI-ACS.

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