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'Evaluating B-type Natriuretic Peptide Levels in Patients with Non-ST Segment Elevation Myocardial Infarction'

[ST Elevasyonu Olmayan Miyokard Enfarktüslü Hastaların B-Tipi Natriüretik Peptid Düzeylerinin Değerlendirilmesi]

Fatma Ucar,
Yuksel Koca,
Gonul Erden,
Turan Turhan,
Mustafa Metin Yıldırımkaya,
Serpil Erdogan,
Zeynep Ginis

Department of Clinical Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey

Yazışma Adresi
[Correspondence Address]

Gonul ERDEN, MD,

Ankara Numune Hastanesi Cebeci Merkez Laboratuvarlari,
06340 Ankara, Turkey.
E-mail: drgonulerden@gmail.com
Phone Number: +90 312 3621487
+90 538 3262970
Fax Number: +90 312 3623972

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ABSTRACT

Background: We compared the B-type natriuretic peptide levels in patients with non ST-segment elevation myocardial infarction, with the levels in the healthy control group.

Methods: A prospective study was conducted in the emergency department. Thirty patients with non ST-segment elevation myocardial infarction and 29 healthy control subjects were included in the data analysis. We sampled B-type natriuretic peptide at up to 3 time points within 72 h of presentation (0-24, 24-48 and 48-72 hours) and the testing was performed using microparticle enzyme immunoassay method.

Results: Median B-type natriuretic peptide, cardiac troponin I and creatine kinase MB levels were significantly higher in patients with non ST-segment elevation myocardial infarction than control group ($p<0.05$). According to the receiver operating curve analysis; area under the curve calculated for cardiac troponin I, creatine kinase MB and B-type natriuretic peptide (0-24 h), (24-48 h), (48-72 h) were 0.980, 0.973, 0.640, 0.660, and 0.644 respectively. We found a weak correlation between B-type natriuretic peptide (24-48 h) and both troponin I ($r=0.321$, $p<0.05$) and creatine kinase MB ($r=0.347$, $p<0.01$) levels.

Conclusions: B-type natriuretic peptide does not look as a valuable test for the diagnosis of non ST-segment elevation myocardial infarction. It might be a useful adjunct to standard cardiac markers in patients with non ST-segment elevation myocardial infarction. Further larger scaled studies are required.

Key Words: Non-ST segment elevation myocardial infarction; brain natriuretic peptide; cardiac troponin I; creatine kinase MB; natriuretic peptides.

ÖZET

Amaç: Bu çalışmada, ST segment elevasyonu olmayan miyokard infarktüslü hastalardaki B-tipi natriüretik peptid düzeyleri ile sağlıklı kontrol grubundaki düzeyler karşılaştırılmıştır.

Gereç ve Yöntemler: Çalışmaya ST segment elevasyonu olmayan miyokard infarktüsü tanısı konulan 30 hasta ve 29 sağlıklı kişiden oluşmuş kontrol grubu dahil edilmiştir. Hastaların acile başvurduktan sonraki ilk 72 saatte 3 defa (0-24., 24-48. ve 48-72. saatteki) B-tipi natriüretik peptid düzeyleri ölçülmüştür. Bu ölçümler, mikropartikül enzim immün analiz yöntem ile yapılmıştır.

Bulgular: ST segment elevasyonu olmayan miyokard infarktüslü hasta grubunda ortanca B-tipi natriüretik peptid, kardiyak troponin I ve kreatin kinaz MB düzeyleri kontrol grubuna göre anlamlı olarak yüksekti ($p<0.05$). Yapılan nispi işlemleme özelliği analizine göre troponin I için eğri altında kalan alan 0.980, kreatin kinaz MB için 0.973, B-tipi natriüretik peptid (0-24. saat) için 0.640, (24-48. saat) için 0.660 ve (48-72. saat) için ise 0.644 olarak hesaplanmıştır. B-tipi natriüretik peptid (24-48. saat) ile hem troponin I ($r=0.321$, $p<0.05$) hem de kreatin kinaz MB ($r=0.347$, $p<0.01$) arasında zayıf derecede korelasyon bulunmuştur.

Sonuçlar: B-tipi natriüretik peptid düzeylerinin, ST segment elevasyonu olmayan miyokard infarktüslü hastalarda, tanısal açıdan anlamlı bir yeri olmadığı, diğer parametrelerle kombine kullanımının bir yeri olabileceği ve bu konu ile ilgili daha geniş çaplı araştırmaların yapılması gerektiği sonucuna varılmıştır.

Anahtar Kelimeler: ST elevasyonu olmayan miyokard infarktüsü, B-tipi (beyin) natriüretik peptid, troponin I, kreatin kinaz MB

Introduction

B-type natriuretic peptide (BNP; Brain natriuretic peptide) is a 32-amino acid peptide belonging to the natriuretic peptide family (1). Natriuretic peptides are vasoactive hormones secreted by the heart as part of a systemic response to cardiac stress and ventricular dysfunction. The precursor peptide of BNP is stored in granules of ventricular myocytes. There, it is cleaved to an amino-terminal product (NT-proBNP) and the physiologically active BNP (2). Release of BNP and NT-proBNP are regulated by ventricular wall stress and myocyte stretch (2, 3).

Natriuretic peptides, which have primarily been devoted to the diagnosis, prognosis and response to treatment of congestive heart failure (CHF) (4,5,6), have also been found to be elevated on set of acute coronary syndromes (ACS) (4,7,8). It is now clear that plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated soon after acute myocardial infarction (AMI) (9). As the utility of BNP and NT-proBNP in ACS is still evolving, there is a continued search for the rationale of BNP in diagnosis and prognosis of ACS. There are not many published studies evaluating BNP levels in patients with non-ST segment elevation myocardial infarction (NSTEMI).

Bassan et al evaluated the diagnostic role of admission plasma BNP for AMI in patients presenting to the emergency department with chest pain suggestive of cardiac ischemia without ST-segment elevation. They reported that BNP was a strong predictor of AMI, particularly in patients with chest pain and non-diagnostic ECG and creatine kinase MB (CKMB)/troponin blood levels (10).

In this study, we evaluated the plasma levels of BNP in patients presenting to the emergency department with acute chest pain and with no ST-segment elevation. We sought to characterize the diagnostic utility of the BNP levels at 3 time points within 72 h of presentation (0-24, 24-48 and 48-72 hours). We also investigated the correlation between BNP, cardiac troponin I (cTnI) and CKMB levels.

Methods And Materials

Study population:

From December 2004 through February 2005, we examined 37 patients presenting with chest pain to the emergency department at the Ankara Numune Training and Research Hospital and in whom the admission electrocardiogram did not present ST-segment elevation. The inclusion criteria was having the diagnosis of NSTEMI. Diagnosis of AMI was based on the rise and fall of troponin and CKMB with at least one of the following: ischemic symptoms, electrocardiographic (ECG) changes, or coronary artery intervention (11). Patients with ST segment depression, T wave inversion, or no ECG abnormalities were defined as having NSTEMI (12). Exclusion criteria was; Patients with congestive heart failure (class 3-4, according to New York Heart Society Classification), severe valve disease, a prior MI, known coronary artery disease, chronic renal failure, end stage renal disease. This study finally included 29 healthy controls (10 women and 19 men, mean age: 55.9±6.7 years) and 30 patients with (9 women and 21 men, mean age: 57.4±9.5 years) NSTEMI. Patients with complaints of chest pain were randomly selected from our emergency department. All patients underwent standard 12-lead ECG immediately after admission, and blood samples were taken for biochemical measurements. Final diagnoses were assigned for all patients by the same cardiologist based on patient history, biochemical data, and diagnostic procedures. These patients were managed in coronary care unit. The results of BNP were blinded to the treating physicians.

Age and gender matched healthy controls were randomly selected from our check-up clinic. Counter blood counts, routine biochemical analyses, physical examinations were performed for the individuals from control group. All were questioned for any acute or chronic illness or familial disorder. Apparently healthy individuals were included into the control group. Individuals with congestive heart failure or any chronic disease, severe valve disease, a prior MI, known coronary artery disease, chronic renal failure, end stage renal disease were excluded from the control group.

The study was approved by the local ethics committee, and patients gave informed consent.

Biomarker sampling:

We sampled BNP at up to 3 time points within 72 h of presentation (0-24, 24-48 and 48-72 hours). Troponin I, CK-MB were sampled at 0 to 6 h after presentation.

Biochemical analysis:

For BNP measurements, samples were taken into EDTA-anticoagulated tubes. Sample tubes were transported on ice and centrifuged at + 4 ° C at 1800 *g* for 5 min. The plasma samples were stored in aliquots at -20ºC until testing at the end of each sampling month. The BNP testing was performed using Axsym System BNP assay (Abbott, USA). Axsym BNP is based on Microparticle Enzyme Immunoassay (MEIA) method. The total CV% range for Axsym BNP assay is 6.5%-9.4%, given by the manufacturer. The analytical sensitivity was < 15 pg/mL. The upper reference limit for heart failure was 100 pg/mL for BNP.

cTnI and CK-MB were immediately analyzed. Samples for cardiac troponin I and creatine kinase-MB tests were collected in plane tubes and were centrifuged at 1500 g for 10 min. cTnI was quantified by use of a sandwich immunoassay based on chemiluminescence technology (Access, Beckman Coulter, USA), and a decision limit of 0.5 ng/mL was used. The total CV% range for Access cTnI assay is 4.3%-6.9%, given by the manufacturer.

The analytical sensitivity was 0.01 ng/mL. The clinical sensitivity of the cTnI assay using a cut-off limit 0.5ng/mL is 96% (13). The analytic range of the assay was 0.01-100 ng/mL and the cut-off limit was 0.5 ng/mL. CK-MB activity was measured using immunoinhibition methods on autoanalyzer (Abbott Aeroset, USA). The total CV% range for CK-MB assay is 2.7%-5.1%, given by the manufacturer. The upper reference limit was 24 U/L for CK-MB. The reference levels are given according to the original package inserts.

Statistical analysis:

All data analyses were performed using The Statistical Package for Social Science for Windows (SPSS 11.5). The normality of the distribution of all variables were assessed by the Kolmogorow-Smirnoff test. Differences between two groups in continuous variables that had a normal distribution were evaluated by Independent-t test and for continuous variables that did not have a normal distribution, Mann-Whitney U test was used. Spearman correlation was used to quantify the relationships. A receiver operating characteristics (ROC) curve was generated and the area under the curve (and its 95% CI) was calculated to identify the cut-off value of BNP. In order to investigate the diagnostic value of BNP in NSTEMI; sensitivity, specificity, positive and negative predictive values were estimated in the usual manner. ROC curves were generated and the AUC was calculated for CK-MB and TnI. A probability (p) value of less than 0.05 was considered statistically significant. Variables were expressed as mean ± SD or median (25 % to 75 % quartiles).

Results

Age and gender distribution did not differ between the NSTEMI and control groups. Biochemical characteristics and age of study population (the patients and the control group) are given in Table 1. Median BNP, cTnI and CKMB levels were significantly higher in patients with NSTEMI than control group ($p<0.05$).

ROC curve analysis for BNP, cTnI, CK-MB is shown in Figure 1. According to the ROC curve analysis, only the area under the curve (AUC) for 24-48 h BNP levels were found significant (AUC=0.660, p=0.035). For this reason sensitivity and specificity estimations for 0-24h BNP and 48-72h BNP levels were not performed.

Estimated area under the curve, p value and the confidence interval for BNP, cTnI and CK-MB are given in Table 2. Three different cut-off values were selected for BNP 24-48 hours; (i) 20 pg/mL, (ii) 100 pg/mL and (iii) 150 pg/mL. Sensitivity, specificity and predictive values for the selected cut-off values are given in Table 3.

The results of correlation analysis among cTnI, CK-MB and BNP are given in Table 4. 0-24, 24-48, 48-72 hours BNP levels were compared with the CK-MB levels by accepting TnI assay as the gold standard in diagnosis.

Table 1. Biochemical characteristics and age of study population
Values for BNP, cTnI, CKMB are median (25% percentile to 75% percentile), and means ± S.D. for age.

	NSTEMI PATIENTS (n=31)	CONTROLS (n=29)	P value
Age (yr)	57.4 ± 9.5	55.9 ± 6.7	P=0.25
BNP(0-24h) (pg/mL)	78 (48-131)	50 (27-87)	P=0.04
BNP(24-48h) (pg/mL)	89 (38-192)	50 (27-87)	P=0.007
BNP(48-72h) (pg/mL)	86 (44-128)	50 (27-87)	P=0.03
cTnI (ng/mL)	3.8 (1.5-10.8)	0.01 (0-0.01)	P<0.001
CKMB(U/L)	72 (46-199)	18 (15-21)	P<0.001

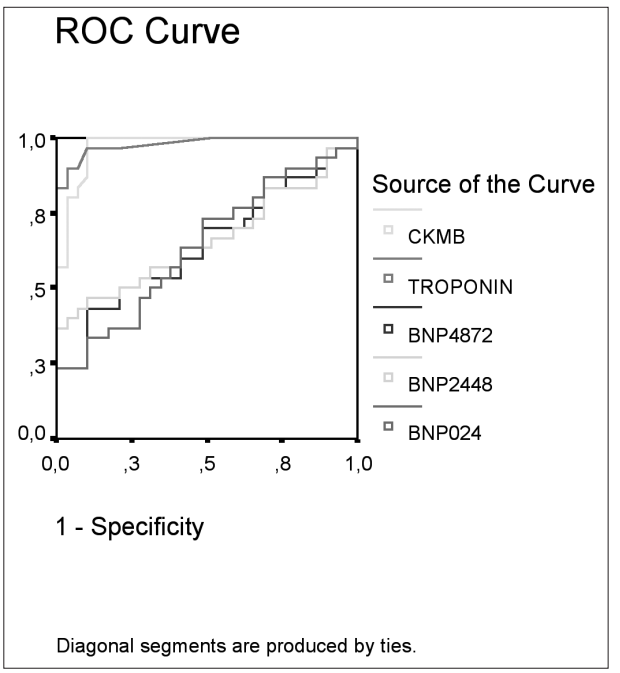

Figure 1. ROC curve analysis of BNP, cTnI and CK-MB as a test concerning the diagnosis of NSTEMI.

As expected, serum levels of cTnI and CK-MB correlated closely ($r=0.80$; $p<0.01$), whereas the correlations between circulating BNP (24-48h) and cTnI ($r=0.321$; $p<0.05$) and BNP (24-48 h) and CK-MB ($r = 0.347$, $p<0.01$) were weak.

Discussion

Diagnosis of acute MI is based on the rise and fall of troponin or creatine kinase-MB with at least one of the

Table 2. Estimated area under the ROC curve, p value and the 95% confidence interval for BNP, cTnI and CK-MB levels.

	Area under the curve (AUC)	P value	*95% CI*
BNP(0-24h)	0.640	0.064	0.499-0.781
BNP(24-48h)	0.660	0.035	0.517-0.802
BNP(48-72h)	0.644	0.058	0.502-0.786
cTnI	0.980	<0.001	0.951-1.009
CK-MB	0.973	<0.001	0.937-1.009

following: ischemic symptoms, electrocardiographic (ECG) changes, or coronary artery intervention (14).

Patients with non-ST elevation ACS represent a diverse population (15). Non-ST elevation AMI is diagnosed by time-dependent rise of myocardial necrosis markers. Although the tissue specificity of cardiac troponins have improved the ability to make an accurate diagnosis, there is a continued search for optimal markers for ACSs (16). The present study focused on the assessment of BNP [(0-24), (24-48), (48-72)h] to aid in the diagnosis of NSTEMI patients.

This is one of only a few studies that have measured BNP serially over the course of NSTEMI. Previous studies have demonstrated plasma BNP elevation in patients with AMI, reflecting a biphasic behavior in those with large infarct and/or significant systolic dysfunction (2). BNP has been found to increase in the setting of MI (2, 8).

Table 3. Sensitivity, specificity, and predictive values of plasma BNP (24-48h) for the prediction of non-ST segment elevation MI.

Cut-off value(BNP/24-48h)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
20 pg/mL	86.7	16.7	50.9	55.6
100 pg/mL	38.5	76.1	75	40
150 pg/mL	17.1	100	100	46.3

Table 4. The correlation coefficients (r) for the parameters.

		BNP(24-48h)	BNP(48-72h)	cTnI	CKMB
BNP(0-24h)	Patients	0.676**	0.588**	0.339	0.319
	Control			-0,330**	-0.120
	Total	0.829**	0.799**	0.224	0.252
BNP(24-48h)	Patients		0.748**	0.501**	0.490**
	Control			-0.330	-0.120
	Total		0.857**	0.321*	0.347**
BNP(48-72h)	Patients			0.331	0.399*
	Control			-0.330	-0.120
	Total			0.239	0.296*
cTnI	Patients				0.808**
	Control				-0.132
	Total				.805**

* $p<0.05$
** $p<0.01$

Bassan et al were the first to demonstrate significantly elevated plasma BNP levels in patients with NSTEMI on arrival at the emergency department with chest pain compared with unstable angina and non-acute coronary syndrome. When compared with CKMB and troponin I on admission, BNP was more sensitive for the ACS diagnosis with a similar high negative predictive value (10). When measured in association with these necrosis markers on admission, BNP levels added significantly to their diagnostic performance (10). They reported that, BNP, while not a diagnostic tool for AMI, is a strong predictor of it, particularly in patients with chest pain and non-diagnostic ECG and CKMB/troponin blood levels (10). In the present study, we found that a baseline BNP (assayed in the first 0-24h) assessment was not helpful when assessing for ACS diagnosis.

Jernberg et al collected blood samples of patients with acute chest pain without ST-segment elevation upon admission to their coronary care unit and demonstrated a significant trend in the rate of AMI diagnosis across BNP level quartiles (17). Patients with AMI had significantly higher median BNP levels than patients with unstable angina or non-cardiac chest pain (17).

Our results partly confirm previous findings. In the present study median BNP, cTnI and CKMB levels were significantly higher in patients with NSTEMI than in the control group. However, according to the ROC curve analysis, only the area under the curve for 24-48 h BNP levels were found significant (AUC=0.660, p=0.035). This means a delay in diagnosis. So BNP may be an adjunct to standard cardiac markers.

In this study, for BNP (24-48 h) of >100 pg/mL as cut-off value, we found 38% sensitivity and 76% specificity. In the study of Bassan et al, elevated BNP of >100pg/mL at time of admission was found to be 70% sensitive and 68% specific for acute MI in patients with NSTEMI (10).

In a study evaluating the diagnostic and prognostic utility of short-term (within 24 hours of presentation) dynamic changes in natriuretic peptides (BNP and NT-proBNP) in patients presenting with chest pain: Natriuretic peptides were diagnostic for congestive heart failure (CHF) and new on-set CHF but less so for ACS. Serial sampling did not improve the prognostic value of BNP or NT-proBNP (16).

Gill et al found a modest, but statistically significant correlation between maximum NT-BNP and maximum CKMB levels(r=0.435, p=0.038) (18). There were no other significant correlations between maximum natriuretic peptide levels and maximum TnT, CKMB and myoglobin in a group of ST segment elevation acute MI patients (18). However, we found a weak correlation between BNP (24-48h) and cTnI (r=0.321; p<0.05) in a group of non-ST segment elevated acute MI patients.

Similar with our findings, Panteghini et al (19) found a positive correlation between plasma BNP concentrations and peak CKMB (r=0.40, p=0.001) in a group of 64 AMI patients.

The main limitation of our study is the relatively small number of patients studied.

A meta-analysis of all data available for the evaluation of the diagnostic value of natriuretic peptide assays in ACS is difficult due to some problems. The first problem is that there is a few study connected with diagnostic value of BNP and its use in combination with other biochemical markers in literature. A second problem is that there is no nomenclature for cardiac natriuretic peptides universally accepted and used in the literature. Lack of standardization for these peptides as well as use of the same units, references, and cut-off values is another problem. There are insufficient results concerning which hormone (ANP or BNP) or N-terminal pro-peptide (Nt-proANP or Nt-proBNP) should be assayed. Much work is still needed to assess the diagnostic and prognostic values of BNP in cardiac disease (20, 21).

In conclusion, our data did not encourage the usage of BNP for the diagnosis of non ST-segment elevation myocardial infarction. Clinically, BNP had a very limited value when compared with cTnI.

Although the diagnostic value of BNP in patients with ACS did not look so promising, further researches about its use in combination with other biomarkers may be considerable. The ideal time for BNP sampling and the detection of a cut-off limit value as an adjunct to standard cardiac markers for ACS may be evaluated in further studies.

References

[1] Stein BC, Levin RI (1998) Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. Am Heart J 135:914-23.

[2] Morita E, Yasue H, Yoshimura M (1993) Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation 88:82-91.

[3] Hama N, Itoh H, Shirakami G (1995) Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 92:1558-64.

[4] McCullough PA, Nowak RM, McCord J (2002) B type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) multinational study. Circulation 106:416-22.

[5] Maisel AS, Krishnaswamy P, Nowak RM (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure.N Engl J Med 347:161-7.

[6] Clerico A, Lervasi G, Del Chicca MG (1998) Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. J Endocrinol Invest 21:170-9.

[7] Karlson BW, Herlitz J, Petterson P, Ekvall HE, Hjalmarsson A (1991)Patients admitted to the emergency room with symptoms indicative of acute myocardial infarction. J Intern Med 230:251-8.

[8] Talwar S, Squire IB, Downie PF (2000) Profile of plasma N-terminal proBNP following acute myocardial infarction;correlation with left ventricular systolic dysfunction.Eur Heart J 21:1514-21.

[9] White M, Rouleau J, Hall C et al (2001). Changes in vasoconstructive hormones, natriuretic peptides, and left ventricular remodelling soon after anterior myocardial infarction. Am Heart J 142:1056-1064.

[10] Bassan R, Potsch A, Maisel A (2005) B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. Eur Heart J 26:234-40.

[11] Alpert J, Thygesen K (2000) for the Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/ American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 21:1502-13.

[12] Ogawa A, Seino Y, Yamashita T, Ogata K, Takano T (2006) Difference in elevation of N-terminal pro-BNP and conventional cardiac markers between patients with ST elevation vs non-ST elevation acute coronary syndrome.Circ J 70:1372-8.

[13] Zweig MH, Campbell G (1993). Receiver-Operating Characteristic (ROC) Plots: A fundamental Evaluation Tool in Clinical Medicine. Clin. Chem 39 (4): 561-577.

[14] Alpert JS, Thygesen K, Antman E, Bassand JP (2000) Myocardial infarction redefined –a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 36:959-69.

[15] Squire I, O'Brien RJ, Demme B, Davies JE, Leong LNG (2004) N-Terminal pro-atrial natriuretic peptide(N-ANP) and N-Terminal pro-B-type natriuretic peptide (N-BNP) in the prediction of death and heart failure in unselected patients following acute myocardial infarction.Clin Sci 107:309-16.

[16] Kwan G, Jackson SR, Beede J, Clapton P, Maisel AJ, Fitszgerald RL (2007) Short –term serial sampling of natriuretic peptides in patients presenting with chest pain. J Am Coll Cardiol 49(11):1186-92.

[17] Jernberg T, Stritsberg M, Venge P (2002) N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am Coll Cardiol 40:437-45.

[18] Gill D, Seidler T, Troughton RW, Yandle TG, Frampton CM (2004) Richards M, Lainchbury JG Nicholls G. Vigorous response in plasma N-terminal pro-brain natriuretic peptide (NT-BNP) to acute myocardial infarction. Clin Sci 106:135-9.

[19] Panteghini M, Cuccia C, Bonetti G, Pagani F, Giubbini R, Bonini E (2003) Rapid determination of brain natriuretic peptide in patients with acute myocardial infarction. Clin Chem Lab Med 41(2):164-8.

[20] Plebani M. (2001) Biochemical markers of cardiac damage: from efficiency to effectiveness. Clin Chim Acta 311:3-7.

[21] Clerico A, Emdin M (2004) Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: A review. Clin Chem 50(1):33-50.