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ARAŞTIRMA MAKALESİ

The Relationship Between N-Terminal Pro-Brain Natriuretic Peptide Level and Myocardial Performance Index and Their Prognostic Importance in Patients With Acute ST-Elevation Myocardial Infarction in Short Term Follow-up

Akut ST Elevasyonlu Miyokard İnfarktüsü Olan Hastaların Kısa Dönem Takibinde N-Terminal Pro-Beyin Natriüretik Peptit Düzeyi ve Miyokard Performans İndeksi arasındaki İlişki ve Bunların Prognostik Önemleri

Running head: NT - ProBNP and MPI in STEMI

Mehmet Küçükosmanoğlu*, Cihan Örem

Abstract: **Introduction:** MPI is an echocardiographic parameter that exhibits the left ventricular functions globally. NT-proBNP is an important both diagnostic and prognostic factor in heart failure. In this study, we aimed to investigate the prognostic significance of serum NT-proBNP levels and MPI in patients with STEMI.

Method: Totally, 104 patients with a diagnosis of STEMI were included in the study. Patients were followed for 30-days and questioned for the presence of symptoms of heart failure (HF) and cardiac death. Patients were invited for outpatient control after 30-days and were divided into two groups: (HF (+) group) and (HF (-) group).

Results: Totally, 104 patients with STEMI were hospitalized in the coronary intensive care unit. Of those patients, 17 were female (16%), 87 were male (84%), and the mean age of the patients was 58.9±10.8 years. During the 30-day follow-up, 28 (27%) of 104 patients developed HF. The mean age, hypertension ratio, and anterior STEMI rate were significantly higher in the HF (+) group compared to the HF (-) group. Ejection time (ET) and left ventricular ejection fraction (LVEF) were significantly lower, and MPI was significantly higher in the HF (+) group. When the values on day first and sixth were compared, NT-ProBNP levels were decreased in both groups. There was no significant difference between the two groups in terms of the change in MPI values on the first and sixth days. Multiple regression analyses showed that the presence of anterior MI, first-day NT-proBNP level, and LVEF were independently associated with the development of HF and death.

Conclusion: In our study, NT-proBNP levels were found to be positively associated with MPI in patients with acute STEMI. It was concluded that the level of NT-proBNP, especially on the 1st day, was more valuable than MPI in determining HF development and prognosis after STEMI.

Keywords: Myocardial performance index, ST-elevation myocardial infarction, NT-Pro brain natriuretic peptide

Öz: **Giriş:** MPİ sol ventrikül fonksiyonlarını global olarak yansıtan ekokardiyografik bir parametredir. NT-proBNP kalp yetmezliği (KY) hastalarında hem diagnostik hem de prognostik önemli bir faktör olduğu birçok çalışmada gösterilmiştir. Biz bu çalışmada STEMİ geçiren hastalarda NT-proBNP seviyesinin ve MPİ' nin prognostik önemini araştırmayı amaçladık.

Yöntem: STEMİ tanılı 104 hasta çalışmaya dahil edildi. Hastalar KY semptomları ve kardiyak ölüm gelişimi açısından 30 gün boyunca takip edildiler. Hastalar 30 gün sonra kontrole çağırıldılar ve KY (+) grubu ve (KY (-) grubu olarak iki gruba ayrıldılar.

Bulgular: STEMİ tanılı toplam 104 hasta koroner yoğun bakım ünitesine yatırıldı. Hastaların 17' si kadın (%16), 87' si erkekti (% 84). Hastaların yaş ortalaması 58.9±10.8 idi. 30 günlük takip boyunca 104 hastanın 28' inde (% 27) KY gelişti. Ortalama yaş, hipertansiyon ve anterior STEMİ sıklığı KY (-) grup ile kıyaslandığında KY (+) grupta anlamlı olarak daha yüksekti. KY (+) grupta sol ventrikül ejeksiyon fraksiyonu (SVEF) ve ejeksiyon zamanı anlamlı olarak düşük, MPİ ise anlamlı olarak daha yüksekti. 1. ve 6. günlerdeki değerler karşılaştırıldığında NT-proBNP seviyesinin her iki grupta da düşmüş olduğu izlendi. 1. ve 6. günlerdeki MPİ değerlerindeki değişim açısından bakıldığı zaman her iki grup arasında anlamlı bir fark yoktu. Çoklu regresyon analizinde, ön duvar STEMİ varlığı, 1. gün NT-proBNP seviyesi ve SVEF KY ve ölüm gelişimi ile bağımsız olarak ilişkili bulundu.

Sonuç: Çalışmamızda akut STEMI'li hastalarda NT-proBNP düzeyleri ile MPİ pozitif ilişkili bulunmuştur. Özellikle 1. günde saptanan NT-proBNP düzeyinin STEMİ sonrası KY gelişimini öngördürmede ve prognozu belirlemede MPİ'dan daha değerli olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Myokard performans indeksi, ST elevasyonlu myokard infarktüsü, NT-Pro beyin natriüretik peptid

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This study was prepared by rearrangement of the speciality thesis by the first author. The ethical consent was obtained from the Clinical Ethical Committee of The Black Sea Technical University and Helsinki Declaration rules were followed to conduct this study.

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1. INTRODUCTION

Almost one-third of the total deaths in Turkey are caused by coronary artery diseases (CAD) (1). Most of CAD related deaths develop due to ST-elevation acute myocardial infarction (STEMI). Almost 20% of patients with STEMI die before arriving at the hospital. The mortality rate varies between 5-15% in patients who are hospitalized. Annual mortality after discharge is between 6-10%, and more than half of those patients die due to new developing heart failure after STEMI (2).

There are many clinical and laboratory prognostic factors used in determining the mortality risk in patients with STEMI, such as demographic, electrocardiographic, biochemical, echocardiographic, hemodynamic, and angiographic factors (3-5).

The B-type natriuretic peptide (BNP) is a neurohormone made up of 32 amino acids released from the ventricles due to volume loading and myocardial pressure increase. Prepro-BNP containing 132 amino acids is synthesized first. Later, prepro-BNP turns into ProBNP containing 108 amino acids. ProBNP decomposes by proteolysis into active BNP and inactive N-terminal proBNP (NT-proBNP) containing 76 amino acids.

Many studies have shown that NT-proBNP is an important both diagnostic and prognostic factor in heart failure (6,7, 8). At the same time, BNP has been investigated as a poor prognostic marker, especially related to infarction size, remodeling, and left ventricular dysfunction after STEMI (9).

Echocardiographic studies to determine the risk of mortality after STEMI have focused on left ventricular systolic functions. In STEMI, diastolic functions are known to be impaired as well as systolic functions. However, the 'Myocardial Performance Index', also known as the 'Tei Index', which shows left ventricular functions globally (systolic and diastolic), has been shown to be a sensitive indicator for cardiac dysfunction in patients with congestive heart failure (10). It has been shown to be a useful prognostic factor in heart failure with left ventricular dysfunction, dilated cardiomyopathy, and cardiac amyloidosis (11-14). MPI, as a simply calculated echocardiographic parameter, has been shown to have prognostic significance in patients with STEMI (15,16).

In our study, we aimed to investigate the prognostic significance of serum N-terminal proBNP (NT-proBNP) levels and MPI in patients with STEMI and to investigate the relationship with each other.

2. METHODS

Totally, 104 patients who were admitted to our clinic with a diagnosis of STEMI were included in the study between May 2003 and May 2004. The diagnostic criteria for STEMI were as follows: (I) typical chest pain lasting for more than 30 minutes (II) ST-segment elevation in at least two contiguous leads with the following cut-off points: at least 0.2mV in men or at least 0.15mV in women in leads V2–V3 and/or at least 0.1mV in the other leads or definite/probable a new left bundle branch block. When indicated, right (V3R–V4R) and posterior (V7–V9) derivations were also obtained.

Patients with congestive heart failure (HF), previous myocardial infarction, chronic obstructive pulmonary disease, chronic kidney failure, significant valvular heart disease, and poor echocardiographic image quality were excluded from the study.

The demographic characteristics, clinical and laboratory findings of the patients were recorded. In the first and sixth days of hospitalization, venous blood obtained from all patients to evaluate serum NT-ProBNP levels. The NT-proBNP level was determined by Elecsys proBNP kit (Cat No. 3121666, Roche diagnosis, Mannheimm Germany) by electrochemiluminescence immunoassay method.

Also, transthoracic echocardiography performed for all patients, and MPI values determined. All echocardiographic examinations were performed with Hewlett-Packard SONOS 2500 machine with a 2.5 MHz transducer by an expert cardiologist. The isovolumic relaxation time (IVRT) was measured from the closure of the aortic valve to the opening of the mitral valve. The isovolumic contraction time (IVCT) was measured from the closure of the mitral valve to the opening of the aortic valve. Ejection time (ET) was measured from the opening to the closure of the aortic valve on the LV outflow velocity profile. Tei index was equal to the sum of the IVRT and IVCT divided by the ET (13). To calculate MPI: Diastolic mitral flow patterns were recorded with pulsed wave Doppler in four apical cavity images. The time elapsed between the end of one mitral flow pattern, and the start of the other mitral flow pattern was calculated (A). The duration of the flow pattern taken approximately 1 cm below the aortic valve was determined by pulsed-wave Doppler in four apical cavity images (B). It was calculated using the formula MPI: (A-B) / B (Figure 1).

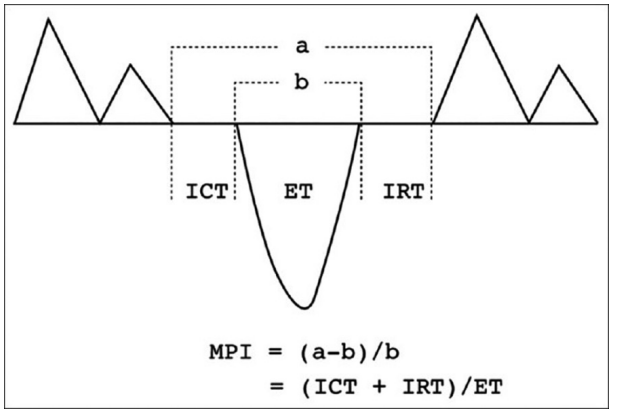

Figure 1. Calculation of MPI.

Patients followed for 30-days and questioned for the presence of symptoms of heart failure (HF) and cardiac death by phone. Patients were invited for outpatient control after 30-days and were divided into two groups: those patients with HF (HF (+) group) and without HF (HF (-) group). Left ventricular ejection fraction (LVEF) less than 40% was used to define HF. Also, NT-proBNP levels, MPI values, and other echocardiographic parameters compared between the groups on the first and sixth days after STEMI.

Ethical Declaration

This study was prepared by rearrangement of the speciality thesis by the first author. The ethical consent was obtained from the Clinical Ethical Committee of The Black Sea Technical University and Helsinki Declaration rules were followed to conduct this study. Patients were informed about the study and written consent forms were signed by all patients prior to inclusion in the study.

2.1 Statistical Analysis

Continuous variables determined as mean (standard deviation). The distribution of variables was analyzed by the Kolmogorov-Smirnov test. Variables with normal distribution compared with Student's t-test and without distribution compared with the Mann-Whitney U test. Variables evaluated first and the sixth day after STEMI compared with the Paired t-test or Wilcoxon test.

Categorical variables presented as % and number and compared with Chi-square or Fisher's exact test. Correlation between variables was examined with Pearson and Spearman correlation tests. To determined independent predictors for the development of HF and death, logistic regression analysis performed. A p value< 0.05 determined as statistically significant.

3. RESULTS

Totally 104 patients with STEMI were hospitalized in the coronary intensive care unit. Of those patients, 17 were female (16%), 87 were male (84%), and the mean age of the patients was 58.9±10.8 years. History of diabetes mellitus (DM) was present in 15 (14%) patients, hypertension (HT) in 44 patients (42%), hyperlipidemia in 19 patients (18%), obesity in 18 patients (17%), and family history of CAD in 27 patients (26%). Totally 61 (59%) of the patients were smokers. Anterior localization STEMI has been detected in 55 (53%) of the patients. Thrombolytic therapy, tissue plasminogen activator (t-PA) 32%, and streptokinase 68%) were received by all patients. During the 30-day follow-up, 28 (27%) of 104 patients developed HF. The general characteristics of patients who developed HF (HF (+) group) and those who did not (HF (-) group) present in Table-1.The mean age (64.5 ± 8.9 vs. 56.8±10.7, p=0.001) and HT ratio (35% vs. 61%, p=0.03) were significantly higher in the HF (+) group compared to the HF (-) group. Anterior STEMI rate was more frequent in the HF (+) group (86% vs. 41% p=0.001).

Table 1. Comparison of baseline demographic and clinical characteristics of study groups.

Variable	HF (+) Group (n=28)	HF (-) Group (n=76)	p
Age, years	64.5±8.9	56.8±10.7	0.001
Gender, female, %	21	14	NS
Obezite (%)	7	21	NS
Hypertension, %	61	35	0.03
Diabetes mellitus, %	21	12	NS
Hyperlipidemia, %	18	18	NS
Smoking, %	57	59	NS
History of CAD, %	25	26	NS
Pain-to-admission, hour	6.5±5.2	5.5±4.0	NS
Pre-infarction angina (%)	18	51	0.005
Anterior wall STEMI (%)	86	41	0.0001
Thrombolytic therapy (%)	36	66	0.01
Pain-to- thrombolytic, hour	3.4±1.2	3.6±l.5	AD
Streptokinase, %	60	70	AD
t-PA, %	40	30	AD
Beta Blocker, %	32	76	<0.0001
ACE inhibitors, %	64	75	AD

CAD: Coronary Artery Disease, STEMI: ST elevation Myocardial Infarction, t-PA: Tissue Plasminogen Activator, ACE: Angiotensin Converting Enzyme

Table 2. Comparison of biochemical parameters of the study groups.

Variable	HF (+) Group (n=28)	HF (-) Group (n=76)	p
The count of leukocytes (/mm^3)	14.728 ± 4.972	12.646 ± 3869	0.05
Serum glucose (mg/dl)	256.8 ± 133.7	156.1 ± 59.7	0.0001
Peak serum CK (mg/dl)	4030 ± 3686	2459 ± 1777	0.01
Peak serum CK-MB (mg/dl)	384.1 ± 272	267.9 ± 198.6	0.04
Serum CRP (mg/dl)	12.9 ± 14	3.1 ± 4.6	0.0001
NT-proBNP level, 1st day (ng/dl)	10.110 ± 8891	1515 ± 1063	0.0001
NT-proBNP level, 6th day (ng/dl)	5916 ± 5843	793 ± 801	0.0001
Total Cholesterol (mg/dl)	184.1±58.5	196.9±44.0	NS
HDL Cholesterol (mg/dl)	39.5±8.9	43.1±9.6	NS
LDL Cholesterol (mg/dl)	129.8±47.4	133.9±40.8	NS
Triglyceride (mg/dl)	137.0±74.5	137.9±81.0	NS

CK: Creatine kinase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NT-proBNP: N-terminal probrain natriuretie peptide, CRP: C reactive protein

There was no significant difference between the two groups in terms of the use of angiotensin-converting enzyme (ACE) inhibitors. The beta-blocker usage rate was lower in the HF (+) group compared to the HF (-) group (32% vs. 76%, p = 0.001). During the follow-up period, 14 (13%) patients died, and all of the patients were in the HF (+) group. The biochemical parameters of both groups presented in Table 2. The count of leukocytes (14.728 ± 4.972 vs. 12.646 ± 3869, p = 0.05) and serum glucose levels (256.8 ± 133.7 mg/dl vs. 156.1 ± 59.7 mg/dl, p=0.0001) were significantly higher in the HF (+) group compared to the HF (-) group.

Peak serum CK and CK-MB levels were significantly higher in the HF (+) group (4030±3686 mg/dl vs. 2459±1777 mg/dl and 384.1±272 mg/dl vs. 267.9±198.6 mg/dl, respectively,p<0.05). In the HF (+) group, both the serum CRP and NT-proBNP levels obtained on the first day were significantly higher than HF (-) group (p<0.05 for both). Similarly, the plasma NT-proBNP level on the sixth day was significantly higher in the HF (+) group than HF (-) group (p<0.05). Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) on the first and the sixth day were significantly higher in the HF (+) group than HF (-) group. On the first day of hospitalization, isovolumetric relaxation time (IVRT) was significantly shorter, and isovolumetric contraction time (IVCT) was significantly longer in the HF (+) group. Ejection time (ET) and LVEF were significantly lower, and MPI was significantly higher in the HF (+) group (Table-3). While there was no significant difference in IVRT on the sixth day of hospitalization between the groups, IVCT was significantly longer in the HF (+) group (Table-4). ET and LVEF were significantly lower in the HF (+) group than HF (-) group. When the values on day first and sixth were compared, NT-ProBNP levels were decreased in both groups. While this decrease was not statistically significant in the HF (+) group, it was statistically significant in the HF (-) group (10.110 ± 8891 ng/dl vs. 5916 ± 5843 ng/dl, p=0.2, 1515 ± 1063 ng/dl vs. 793 ± 801 ng/dl, p=0.0001, respectively). There was no significant difference between the two groups in terms of the change in MPI values on the first and sixth days. Multiple regression analysis showed that the presence of anterior MI [OR= 78.8, CI: 1.16-5310.6; p<0.01], first day NT-proBNP level [OR=1.001, CI: 1.001-1.002; p<0.01) and LVEF [OR = 0.8, CI: 0.64-0.96;p<0.01] were independently associated with development of HF and death (Table 5).

Table 3. Comparison of echocardiographic parameters on 1st day

Variables on 1st day	HF (+) Group (n=28)	HF (-) Group (n=76)	p
LVESV (ml)	84.1 ± 23.8 ml	44.1 ± 20.2	0.0001
LVEDV (ml)	115.7 ± 26.2	85.1 ± 24.4	0.0001
IVRT (ms)	72.1 ± 30.1	76.0 ± 15.0	0.03
IVCT (ms)	84.4 ± 25.1	45.7 ± 29.0	0.0001
ET (ms)	219.0 ± 40.4	269.3 ± 31.3	0.0001
LVEF (%)	27.4 ± 8.0	49.7 ± 10.5	0.0001
MPI	0.75 ± 0.20	0.46 ± 0.16	0.0001

LVESV: Left ventricular end systolic volume, LVEDV: Left ventricular end diastolic volume, IVRT: Isovolumetric relaxation time IVCT: Isovolumetric contraction time, ET: Ejection time, LVEF: Left ventricular ejection fraction, MPI: myocardial performance index

Table 4. Comparison of echocardiographic parameters on 6th day

Variables on 6th day	HF (+) Group (n=28)	HF (-) Group (n=76)	p
LVESV (ml)	77.0 ± 19.5 ml	44.9 ± 21.9	0.0001
LVEDV (ml)	109.5 ± 23.6	87.8 ± 25.8	0.0001
IVRT (ms)	78.9±29.0	81.1±14.8	NS
IVCT (ms)	84.4±30.0	40.1±25.2	0.0001
ET (ms)	225.8 ± 24.3	274.1 ± 27.7	0.0001
LVEF (%)	29.9 ± 6.9	50.0 ± 10	0.0001
MPI	0.73 ± 0.16	0.45 ± 0.14	0.0001

LVESV: Left ventricular end systolic volume, LVEDV: Left ventricular end diastolic volume, IVRT: Isovolumetric relaxation time IVCT: Isovolumetric contraction time, ET: Ejection time, LVEF: Left ventricular ejection fraction, MPI: myocardial performance index

Table 5. Regression analysis results showing the relationship between development of HF and death with prognostic factors.

	P	Exp(B)	%95 CI
Age	0.08	1.2	0.97-1.46
DM	0.25	12.7	0.16-985.7
Anterior MI	0.04	78.8	1.16-5310.6
Thrombolytic therapy	0.5	2.7	0.14-53.3
CK-MB	0.81	0.9	0.9-1.006
CRP	0.63	0.93	0.69-1.24
NT- ProBNP on 1st day	0.05	1.001	1.001-1.002
MPI on 1st day	0.13	1.05	0.98-1.12
LVEF on 1st day	0.02	0.8	0.64-0.96

DM: Diabetes mellitus, MI: Myocardial infarction, CK-MB: Creatine kinase – MB, NT-ProBNP: N terminal – Pro brain natriuretic peptide, MPI: Myocardial performance index, LVEF: Left ventricular ejection fraction

4. DISCUSSION

In the present study, we shorn that the severity of left ventricular dysfunction is the most important predictor of poor prognosis after STEMI. Also, left ventricular MPI and BNP are poor prognostic factors related to LV dysfunction after STEMI. Moreover, we found that MPI was positively correlated with NT-proBNP levels in the first and the sixth day after STEMI.

There are several studies in which the prognostic significance of BNP and MPI are evaluated individually. In many studies, BNP has been shown to be more valuable than LVEF and clinical parameters in determining prognosis in HF patients (18,19). It has also been found that increased serum BNP levels after STEMI can identify patients at high risk for death and heart failure, regardless of age, LVEF, and history of heart failure (20,21). In STEMI, serum BNP level increases rapidly from the first day (17,18). In most studies, serum BNP levels measured between 2th and 7th days after STEMI have been shown to be associated with poor prognosis (17,19, 21-24). In our study, we found that NT-proBNP, which was measured on the first and sixth days after STEMI, was significantly higher in patients with HF. In addition, NT-ProBNP level decreased between first and sixth days after STEMI in all patients, and this decrease was found to be significant only in patients who did not develop HF. The decrease in the NT-ProBNP level in the HF (+) group was not statistically significant. Our results regarding the prognostic significance of NT-proBNP after acute STEMI are consistent with the literature.

Ono et al. showed that MPI was positively associated with BNP levels in a group of 74 patients with various heart diseases. In the same study, other echocardiographic parameters were shown to be significantly associated with BNP (17). Foy et al. reported a significant correlation between LVEF and serum BNP levels on the fifth day and third month after STEMI (25). In a study involving 799 patients with acute STEMI, Moller et al. showed that the restrictive filling pattern and increased MPI observed in the first 6-days were independent predictors of all-cause deaths (15). In another study involving 96 patients, MPI calculated on the first day of acute STEMI was shown to be an independent predictor in predicting in-hospital cardiac events (26).

In our study, the MPI values observed on the first and sixth days showed significant relationships with other prognostic factors. Despite the significant results obtained in single analyzes, the independent relationship of MPI with HF and death development was not detected in multiple regression analyses. In addition, although there was a significant decrease in NT-proBNP level between the first and sixth days in the HF (-) group, the change in MPI levels was not significant. This situation predicts that NT-proBNP is more valuable than MPI in predicting HF development.

5. CONCLUSION

In our study, NT-proBNP levels were found to be positively associated with MPI in patients with acute STEMI. At the same time, it has been observed that NT-proBNP and MPI are significantly related to many demographic, biochemical, and echocardiographic prognostic factors. It was concluded that the level of NT-proBNP detected, especially on the 1st day, was more valuable than MPI in determining HF development and prognosis after STEMI.

5.1 Limitations

Our study has several limitations. First, this was a single-center study, and the sample size was small. Second, a percutaneous coronary intervention, which is the main

strategy in treatment in STEMI, was not used due to technical deficiencies.

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