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## RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

# The relationship between myocardial viability and plasma NT-proBNP levels

# Miyokard canlılığı ve plazma NT-proBNP düzeyleri arasındaki ilişki

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ABSTRACT

Aim: There is no biochemical marker that indicates myocardial viability in the late phase after myocardial infarction. The aim of our study was to identify whether plasma NT-proBNP levels indicate the presence of viable myocardium after myocardial infarction.

Material and Methods: Patients with myocardial infarction and left ventricular ejection fraction of less than 45% were included in the study. Exercise or pharmacological myocardial perfusion scintigraphy was performed to investigate viability in the infarction region. The left ventricle was divided into 19 segments where the necrotic area and viable myocardium within it was measured. Blood samples for NT-proBNP measurement were obtained from all patients on the same day scintigraphy performed.

Results: A total of 60 patients were included in the study (10 females, 50 males, mean age 62 ± 9 years). 48 (80%) patients underwent exercise scintigraphy. The mean exercise time was 7.1 ± 2.3 minutes. The infarct area was located in anterior segments in 16 patients, inferior in 25, and in both locations in 19 patients. The mean left ventricular ejection fraction was 36 ± 8%. There was a negative correlation between left ventricular ejection fraction and serum NT-proBNP levels ($r = -0.03$ $p < 0.01$). On the other hand, there was no correlation between plasma NT-proBNP levels and the presence or extent of viable myocardium within the necrotic area ($P = 0.8$).

Conclusion: There was no correlation between plasma NT-proBNP levels and the presence of viable myocardium in the infarct zone in patients with myocardial infarction.

Keywords: myocardial infarction, viable myocardium, NT-proBNP, myocardial perfusion scintigraphy

ÖZET

Amaç: Miyokard enfarktüsü sonrasında enfarkt bölgesindeki rezidü miyokard canlılığını gösteren herhangi bir biyokimyasal parametre bulunmamaktadır. Çalışmamızda miyokard enfarktüsü sonrası dönemde serum NT-proBNP seviyeleri ile miyokard canlılığı arasındaki ilişkiyi araştırdık.

Metod: Çalışmaya miyokard enfarktüsü geçiren ve sol ventrikül ejeksiyon fraksiyonu %45'in altında olan hastalar alındı. Egzersiz ya da farmakolojik miyokard perfüzyon sintigrafisi yapılarak enfarktüs bölgesinde iskemi ve canlılık araştırıldı. Sol ventrikül toplam 19 segmente bölünerek ilgili nekrotik ve canlı bölgelerin alanı hesaplandı. Serum NT-proBNP ölçümü için tüm hastalardan işlem sabahı serum örnekleri alındı.

Bulgular: Çalışmaya toplam 60 hasta alındı (10 kadın, 50 erkek, ortalama yaş 62±9 yıl). Hastaların 48'i (%80) egzersiz yaptı. Ortalama egzersiz süresi 7,1±2,3 dakika idi. Enfarkt alanı 16 hastada anterior, 25 hastada inferior ve 19 hastada ise her iki bölgedeydi. Hastaların ortalama sol ventrikül ejeksiyon fraksiyonu 36±8 olarak hesaplandı. Sol ventrikül ejeksiyon fraksiyonu ile serum NT-proBNP arasında negatif korelasyon tespit edildi ($r=-0.03$ $p<0.01$). Öte yandan serum NT-proBNP seviyeleri ile enfarkt bölgesindeki canlı ya da iskemik alan arasında bir korelasyon tespit edilmedi ($P=0,8$ ve $0,7$).

Sonuç: Miyokard enfarktüsü geçirmiş kişilerde enfarkt bölgesindeki canlı doku alanı ile serum NT-proBNP seviyeleri arasında ilişki saptanmadı.

Anahtar kelimeler: miyokard enfarktüsü, miyokard canlılığı, NT-proBNP, miyokard perfüzyon sintigrafisi

## Introduction:

In patients with myocardial infarction (MI), left ventricular function is one of the most important factors for prognosis.[1] Various studies has shown that impaired left ventricular function may improve after revascularization.[2] However, it is not always easy to decide whether those with severe LV dysfunction will benefit from coronary revascularization. Therefore, myocardial viability should meticulously be demonstrated before revascularization in such patients. In order to assess myocardial viability in the necrotic area, several imaging modalities like dobutamine stress echocardiography, myocardial perfusion scintigraphy, positron emission tomography, and cardiac magnetic resonance imaging have been used for several years.[3,4] On the other hand, apart from imaging studies, there has been no biochemical marker capable of demonstrating the viable tissue in the late phase after myocardial infarction.

Natriuretic peptides (NP) are neurohormones that are secreted by the ventricular myocardium as a response to pressure and volume overload[5]. BNP is the biologically active form which is


then cleaved into the inactive form called NT-proBNP.[6] There are several areas where natriuretic peptides are used. One of them is heart failure.[7] It is used to diagnose, follow-up and guide heart failure therapy[8]. As new researches are being conducted new indications arise. Today, besides heart failure, NP's are investigated in clinical situations like diastolic dysfunction, valve diseases, pulmonary hypertension and acute coronary syndromes.[9]

The purpose of the study was to investigate whether serum NT-proBNP levels indicate the presence of viable myocardium after MI. We planned to detect post infarction myocardial viability by myocardial perfusion scintigraphy and investigate if there is a relationship between viability and the serum NT-proBNP levels.

**Methods:**

This prospective study group was composed of patients who had applied to our outpatient clinic with a history of myocardial infarction. All patients had some angina complaints and myocardial perfusion scintigraphy imaging was planned to search ischemia by their own physicians. Patients with left ventricular ejection fraction over 45% (assessed by echocardiography), morbid obesity (body mass index > 35 kg/m$^2$), chronic renal failure (estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m$^2$), nonischemic left ventricular dysfunction, chronic obstructive lung disease, severe valvular heart disease, previous stroke, chronic inflammatory disease, and liver dysfunction were excluded from the study. Local ethics committee approved the study and written informed consent was obtained from all patients.

Echocardiography was performed in left lateral decubitis position and standard left parasternal long axis, short axis, apical four chamber and five chamber views were obtained in all patients (Acuson Sequoia, Siemens Medical Solution, Mountain view, CA, USA). eGFR was estimated using the formula of Modification of Diet in Renal Disease (MDRD) as previously defined.[10] Serum samples for measuring NT-proBNP, BUN, creatinine, fasting blood glucose, lipid profiles and complete blood count were taken after 12 hours fasting in the morning of myocardial scintigraphy day. Routine biochemical parameters were studied with commercially available kits. Plasma NT-proBNP samples were collected to a heparin containing Vacuette tubes. After waiting for 5 minutes in the room temperature, all blood samples were centrifuged at 3500 rpm for 10 minutes. We particularly paid attention to prevent hemolysis and samples were stored in -80 C until analysis. After all samples were

collected, plasma NT-proBNP levels were measured using chemoluminescence method with a Immulite 1000-Siemens device ( Siemens medical solutions diagnostics, Deerfield, USA). The results were reported as pg/ml.

*Tc-99m-Sestamibi Imaging Protocol*

Patients discontinued their medications that can effect exercise testing 48 hours before according to the current guidelines. Patients performed exercise testing after a 3-hour fasting and they were not allowed to drink tea/coffee or smoke. All patients underwent a standard exercise test using the Bruce protocol. Blood pressure, heart rate and 12-lead ECG were recorded at rest, during each stage of exercise and at peak exercise and for at least 5 minutes after recovery. The electrocardiogram and ST segment deviation were continuously displayed and measured automatically by a computer assisted system. 10 mCi Tc-99 m-sestamibi was given intravenously to all patients in the maximum exercise. Exercise images were taken 45 minutes after the end of exercise. In patients who were unable to exercise, the test was performed using dipyridamole in which 0.56 mg/kg dipyridamole was administered intravenously and rest perfusion images were acquired in the same manner from both the exercise and dipyridamole patients. For imaging; low energized, large surface, two gamma cameras were placed with 90 degree angle to each other and parallel perforated collimator was used (Apex SPX Cardial Elscint Israel ).

*Assessment of images*

Short axis, horizontal long axis and vertical long axis images were created through computer programs from tomographic images that was acquired by single photon emission computed tomography. Basal, mid and apical segments were evaluated in the horizontal planes, septum apical and lateral walls were evaluated in the long axis vertical planes, anterior, apical and inferior walls were evaluated in the long axis horizontal planes. Perfusion was considered normal when all myocardial sections hold homogenous material in the stress images. If any perfusion defect occurred after stress in any myocardial segment and disappeared after rest images, it was considered as transient perfusion defect, ischemia. If the perfusion defect persisted in the rest images after stress images, it was considered as MI or scar. If the amount of material which is held in the constant defect segments was higher than 40% of normal segments in semiquantitive evaluation of if the defect was lower than 60% , ,t was considered

as viable tissue in the myocardial infarction site. If the perfusion defect which was clear in stress images becomes nearly normal in rest but persisted, then it was considered as ischemia in the myocardial infarction site.

*Statistics*

The continuous variables were expressed as mean and standard deviation. Categorical variables were reported as number and percentages. The Kolmogorov-Smirnov test was used to assess the distribution of the continuous variables. Categorical data was compared by using the chi-square test. The relation between two quantitive variables was compared with Pearson correlation analysis. A p value of <0.05 was considered to be statistically significant.

The statistical analysis was performed using SPSS version 16 (SPSSInc., Chicago, IL, USA)

**Results:**

The study included 60 patients (10 women, 50 men, mean age 62±9.7 years). Baseline clinical characteristics of the study patients are presented in Table 1. 47 (78%) patients had hypertension, 27 (45%) had diabetes mellitus. Mean LV ejection fraction was 36±8%. 48 (80%) patients underwent exercise scintigraphy. The mean exercise time was 7.1 ± 2.3 minutes. Plasma NT-proBNP levels ranged from 150 to 13584 pg/ml ( mean: 1622±2751 pg/ml). The localization of infarction was in anterior segments in 16(26%) patients, inferior in 25 (41%) and both locations in 19 (31%) patients respectively.

Myocardial perfusion scintigraphy results are presented in Table 2. The term anterior and inferior MI represents the patients who had necrotic tissue in both areas. Viable tissue within the infarcted region was detected in 38(63%), ischemia within the necrotic area in 12 (20%), ischemia in 5(8%) and total infarction was seen in 5(8%) patients.

Table 3 shows the correlation analysis between NT-proBNP and several other parameters. There was a statistically significant negative correlation between plasma NT-proBNP levels and LV ejection fraction and exercise duration (r=-0.39, P<0.002 and r=-0.40, p=0.005 respectively) (Figure 1-2). However, there was no significant correlation between the presence or the degree of myocardial viability and plasma NT-proBNP levels (all p>0.05).

**Discussion:**

In our study, we did not find any relationship between plasma NT-proBNP levels and the extent of viable myocardial tissue in the infarct zone in patients with previous myocardial infarction.

In fact, the role of natriuretic peptides goes beyond the diagnosis and treatment of heart failure. Recent studies have demonstrated that B-type natriuretic peptide (BNP) is secreted from hypoxic myocardium, even in the absence of left ventricular dysfunction and thus it might be a marker of myocardial ischemia[11]. Moreover, NP's have been shown to predict adverse cardiovascular outcomes in patients with acute myocardial infarction[12]. Therefore, it has been concluded that ischemic heart disease affects cardiac endocrine function independent of left ventricular function. A strong correlation is demonstrated between NT-proBNP and extent of reversible ischemia even in patients with normal LV functions[13]. This interaction between coronary artery disease and BNP/NTproBNP has been attributed to increased BNP gene expression and release by cardiomyocytes in response to ischemia[11]. So it is suggested that ischemia itself, rather than changes in left ventricular wall stress secondary to ischemia, promotes the release of BNP, but the responsible mechanisms still remain to be elucidated.

There are numerous studies conducted in patients with either acute or chronic ischemia showing a positive correlation between natriuretic peptides and the severity or extent of coronary artery disease.[14] Each study had a different methodology. For instance Sarullo et al found a relationship between serum BNP levels and residual ischemia after reperfusion therapy is ST elevation MI[15]. In this study, patients with protected LVEF (>40%) were investigated in the first month after MI and serum NT-proBNP levels and SPECT findings were compared. However, in our study the average time after MI was not homogenous and LVEF was lower. Zaid et al found a positive correlation between serum BNP levels and extent of ischemia by using the exercise SPECT[16]. Likewise, this study was conducted in patients with normal LV function. However, in our study, we included patients with moderate to severe LV dysfunction with different time periods from the infarction. Probably at this level of LV dysfunction with some degree of remodeling, the total performance of LV seems to be the main factor affecting the NT-proBNP levels. Trying to detect a varying degree of viable area in a big infarcted territory and LV dysfunction is out of proportion to the degree of NT-proBNP levels.

*Limitations of the study*

Small sample size and being a single center study were the main limitations of this study. If we had conducted the study in a much larger population, we might have found a correlation between plasma NT-proBNP levels and amount of viable myocardium within the infarct territory. In addition, Tc-99 m-sestamibi was the agent used for viability study. However, Thallium-201 would be more suitable for viability assessment. Finally, this study did not include the data regarding the occlusion in the infarct related artery and also we did not report viability in terms of percentages.

**Conclusion:**

There is no relationship between myocardial viability in the infarcted area and plasma NT-proBNP levels.

Acknowledgements: None

Conflict of interest: None

**Table 1: Baseline clinical characteristics of the study patients**

| **Patients (n=60)** | **(Mean ± SD) or (%)** |
|---|---|
| Age (years) | 62±9.7 |
| Gender (female) | 10 (16%) |
| Hypertension | 47 (78%) |
| Diabetes mellitus | 27 (45%) |
| Hyperlipidemia | 45 (75%) |
| LVEF (%) | 36±8 |
| BUN (mg/dl) | 19±5 |
| Creatinine (mg/dl) | 0.9±0.2 |
| NT-proBNP (pg/ml) | 1622±2751 (100-13854) |
| Anterior infarction | 16 (26%) |
| Inferior infarction | 25 (41%) |
| Anterior + inferior infarction | 19 (31%) |

**Abbreviations:** BUN: blood urea nitrogen; LVEF: left ventricular ejection fraction

**Table 2: Myocardial perfusion scintigraphy findings**

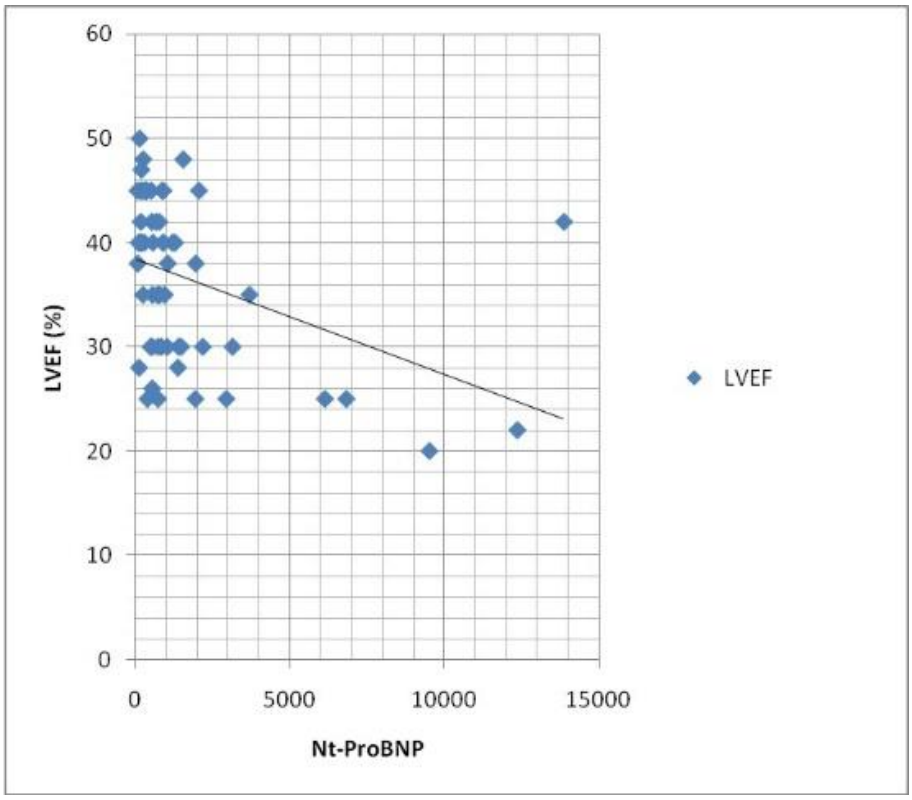
| | Number of patients (%) |
|---|---|
| Viable tissue in the infarction area | 38 (63%) |
| Ischemia in the infarction area | 12 (20%) |
| Pure necrosis | 5 (8%) |
| Ischemia | 5 (8%) |

**Table 3: Correlation between NT-proBNP and several other parameters**

| | R | P |
|---|---|---|
| Age | 0,166 | 0,208 |
| BUN | *0,267* | *0,041* |
| Creatinine | -0,102 | 0,441 |
| LVEF | *-0,392* | *0,002* |
| Ischemia within the infarction area | 0,040 | 0,764 |
| Viable tissue within the infarction area | 0,025 | 0,853 |
| Pure necrosis | -0,013 | 0,923 |
| Exercise duration (minutes) | -0,404 | *0,005* |

**Abbreviations:** BUN: blood urea nitrogen; LVEF: left ventricular ejection fraction

**Figure 1: Correlation between NT-proBNP and left ventricular ejection fraction**



**References**

1. Perelshtein Brezinov O, Klempfner R, Zekry S Ben, Goldenberg I, et al. Prognostic value of ejection fraction in patients admitted with acute coronary syndrome: A real world study. *Medicine (Baltimore)*. 2017; 96: e6226.
2. Singh P, Sethi N, Kaur N, Kozman H. Revascularization in Severe Left Ventricular Dysfunction: Does Myocardial Viability Even Matter? *Clin Med Insights Cardiol*. 2015; 9: 105-109.
3. Yao S-S, Chaudhry FA. Assessment of myocardial viability with dobutamine stress echocardiography in patients with ischemic left ventricular dysfunction. *Echocardiography*. 2005; 22: 71-83.
4. Underwood SR, Bax JJ, vom Dahl J, et al. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. *Eur Heart J*. 2004; 25: 815-836.
5. Ibrahim N, Januzzi JL. The potential role of natriuretic peptides and other biomarkers in heart failure diagnosis, prognosis and management. *Expert Rev Cardiovasc Ther*. 2015; 13: 1017-1030.
6. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail*. 2004; 6: 261-268.
7. Volpe M, Battistoni A, Rubattu S. Natriuretic peptides in heart failure: Current achievements and future perspectives. *Int J Cardiol*. 2019; 281: 186-189.
8. Brunner-La Rocca H-P, Eurlings L, Richards AM, et al. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. *Eur J Heart Fail*. 2015; 17: 1252-1261.
9. Palazzuoli A, Ruocco G, Cekorja B, Pellegrini M, et al . Combined BNP and Echocardiographic assessment in interstitial lung disease for pulmonary hypertension detection. *Int J Cardiol*. 2015; 178: 34-36.
10. Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol*. 1999; 10: 2426-2439.
11. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J Off Publ Fed Am Soc Exp Biol*. 2003; 17: 1105-1107.
12. Mega JL, Morrow DA, De Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy. *J Am Coll Cardiol*. 2004; 44: 335-339.
13. Weber M, Dill T, Arnold R, et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. *Am Heart J*. 2004; 148: 612-620.
14. Oremus M, Raina PS, Santaguida P, et al. A systematic review of BNP as a predictor of prognosis in persons with coronary artery disease. *Clin Biochem*. 2008; 41: 260-265.
15. Sarullo FM, Gristina T, Brusca I, et al. Usefulness of N-terminal pro-B-type natriuretic peptide levels in predicting residual myocardial ischemia in patients with ST elevation acute myocardial infarction. *Minerva Cardioangiol*. 2007; 55: 149-155.
16. Zaid G, Tanchilevitch A, Rivlin E, et al. Diagnostic accuracy of serum B-type natriuretic peptide for myocardial ischemia detection during exercise testing with spect perfusion imaging. *Int J Cardiol*. 2007; 117: 157-164. doi:10.1016/j.ijcard.2006.06.013