Amino Terminal Pro-B-Type Natriuretic Peptide and Late Left Ventricular Reverse Remodeling in Coronary Artery Bypass Grafting Patients with Low Ejection Fraction

Düşük Ejeksiyon Fraksiyonlu Koroner Arter Baypas Greftleme Hastalarında Geç Dönem Sol Ventriküler Revers Remodeling ve Amino Terminal Pro-B-Tip Natriüretik Peptid

Ali Can HATEMİ, MD,[a]
Mete GÜRSOY, MD,[a]
Burcu IŞIKSUNGUR, MD,[a]
Aybala TONGUT, MD,[a]
Işıl UZUNHASAN, MD,[b]
Murat BAŞKURT, MD,[b]
Ayşem KAYA,[c]
Nurhan İNCE, MD,[d]
Serdar KÜÇÜKOĞLU, MD,[b]
Erhan KANSIZ, MD[a]

Departments of
[a]Cardiovascular Surgery,
[b]Cardiology,
[c]Biochemistry Laboratory,
İstanbul University Institute of Cardiology,
[d]Department of Public Health,
İstanbul University
İstanbul Faculty of Medicine,
İstanbul

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Yazışma Adresi/*Correspondence:*
Ali Can HATEMİ, MD
İstanbul University Institute of Cardiology,
Department of Cardiovascular Surgery,
İstanbul,
TÜRKİYE/TURKEY
hatemi@superonline.com

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ABSTRACT Objective: Left ventricular remodeling accelerates the course of cardiac failure by aggravating ventricular dysfunction following myocardial infarction. Thus, prediction and prevention of left ventricular remodeling is crucial. The aim of this study was to evaluate the predictive value of perioperative plasma NT-proBNP levels for postoperative left ventricular reverse remodeling and ejection fraction in patients who underwent coronary artery bypass grafting. **Material and Methods:** Forty patients with myocardial infarction inprevious three months were enrolled in the study. All patients with moderate left ventricular dysfunction (EF ≤40%) underwent on pump coronary artery bypass grafting (CABG) operation. Patients' preoperative left ventricle volumes and indexes, ejection fractions, and NT-proBNP levels were compared to the postoperative values. **Results:** Preoperative NT-proBNP levels were significantly related to preoperative and postoperative ejection fractions, and postoperative left ventricular reverse remodeling (p= 0.037, p= 0.033, p= 0.014, respectively). **Conclusion:** The preoperative N-terminal proBNP may help to assess the postoperative ejection fraction and ventricular remodeling. Amino terminal proBNP is a safe, available and effective tool to predict the postoperative functional and structural changes of the left ventricle.

Key Words: Pro-brain natriuretic peptide (1-76); ventricular remodeling; coronary artery bypass; echocardiography; stroke volume

ÖZET Amaç: İnfarktüs sonrası dönemdeki sol ventrikülün yeniden şekillenmesi (remodelling) kalp yetmezliğine götüren kötü prognoz için güçlü bir göstergedir. Bu çalışmanın amacı perioperatif plazma NT-proBNP düzeyinin cerrahi revaskülarizasyon sonrası sol ventrikül revers remodellingi ve ejeksiyon fraksiyonu yönünden prediktif değerini incelemektir. **Gereç ve Yöntemler:** Son üç ay içinde miyokard enfarktüsü geçiren ve orta düzeyde sol ventrikül (LV) disfonksiyonu olan 40 hasta çalışmaya alındı. Bütün hastalara pompa yardımlı koroner arter baypas greftleme (CABG) operasyonu yapılmıştı. Hastalarda preoperatif sol ventrikül hacimleri ve indeksleri, ejeksiyon fraksiyonları ve NT-proBNP düzeyleri postoperatif değerlerle karşılaştırıldı. **Bulgular:** Preoperatif NT-ProBNP düzeyleri preoperatif ve postoperatif ejeksiyon fraksiyonları ve postoperatif sol ventrikül revers remodelling ile (sırasıyla p= 0.037, p= 0.033, p= 0.014) anlamlı düzeyde ilişkiliydi. **Sonuç:** Preoperatif N-terminal pro-BNP düzeyi postoperatif ejeksiyon fraksiyonu ve ventriküler remodellingi değerlendirmede yardımcı olabilir. Aminoterminal pro-BNP sol ventrikülün fonksiyonel ve yapısal değişikliklerini belirlemek için güvenli, kolayca bulunabilen ve etkili bir araçtır.

Anahtar Kelimeler: Beyin öncesi natriüretik peptid (1-76); ventriküler yeniden yapılanma; koroner arter baypas; ekokardiyografi; atım hacmi

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Measurement of brain natriuretic peptides (BNP) as biochemical markers of cardiac failure is a widely accepted approach.[1-10] In the setting of volume expansion or pressure overload, increasing wall stress stimulates synthesis of pre–proBNP in the ventricular myocardium. The release of BNP results in further myocardial relaxation and exerts an important regulatory role in response to an acute increase in ventricular volume by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin-angiotensin-aldosterone system.[2] Pre-proBNP is cleaved first to proBNP, then to the biologically active BNP and the inactive amino-terminal fragment (NT-proBNP). The slightly wider detection range and the more stable structure of NT-proBNP may favor its use over BNP in the evaluation of patients with left ventricular systolic dysfunction.[1,2] In the last decade, various studies emphasized the use of natriuretic peptides for the diagnosis and treatment monitoring of heart failure.[1,5,6,10-18] Currently, BNP and NT-proBNP are routinely used as diagnostic parameters in many clinics' emergency and intensive care units.Remodeling describes structural changes of heart after myocardial infarction, and can be divided to early and late phases. Early phase occurs within the first three days following myocardial infarction (MI), and the late phase occurs after the third day of MI. Early remodeling affects mainly the infarct and peri-infarct zones, whereas late remodeling includes changes in the shape and size of the entire left ventricle.[21] Echocardiographically, left ventricular (LV) remodeling was defined as more than 15% increase in left ventricle end-systolic diameter,[22] and a decrease of ≥15% in the left ventricle end-systolic diameter (LVESD) is termed as left ventricular reverse remodeling (LVRR).[23] The aim of this study was to assess the correlation between plasma NT-proBNP levels and LVRR in patients with low ejection fraction (EF ≤40%) and recent myocardial infarction (within three months before the CABG operation), undergoing CABG, and the possible use of NT-proBNP level as a follow-up marker of LVRR following CABG.

MATERIAL AND METHODS

STUDY POPULATION

Forty consecutive patients with myocardial infarction in previous three months, with moderate LV dysfunction (EF of ≤40%), and with an indication for a CABG operation were enrolled in study between from January and June 2008 (Table 1). The study was approved by the local ethical committee, and all patients provided informed consent. Exclusion criteria were; concomitant valvular disease, LV aneurysm, perioperative MI, previous cardiac

TABLE 1: Demographic, echocardiographic, and surgical data of the patients. (Patients were grouped and named according to LVVR occurrence, based on LVESVI values.)

	Group I	Group II	P Value	Test
Age (y)	61.85 ± 9.22	62.45 ± 7.81	0.825	t test
Gender (f/m)	4/20	4/20	1	Fisher test
Diabetes mellitus	13/20	7/20	0.102	Fisher test
Preoperative EF (%)	38.20 ± 5.71	40.55 ± 6.14	0.218	t test
Preoperative LVESVI (ml/m^2)	48.51 ±17.87	48.81 ± 17.04	0.956	t test
Preoperative NT proBNP (pg/ml)	1315.12 ± 1495. 78	1244.00 ± 1093.70	0.481	t test
Postoperative EF (%)	42.95 ± 8.82	42.95 ± 10.93	1	t test
Postoperative LVESVI (ml/m^2)	52.70 ± 16.15	38.01 ± 12.37	0.003	t test
Postoperative NT proBNP (pg/ml)	1532.21 ± 2080.58	817.40 ± 749.64	0.01	t test
Mean graft number (n)	3.45 ± 1.05	3.70 ± 0.80	0.327	Mann Whitney U
Mean CPB time (min)	124.70 ± 37.11	146.05±30.15	0.053	t test
Mean cross clamp time (min)	60.25 ± 25.97	74.30 ± 19.40	0.061	t test

LVRR: Left ventricular reverse remodeling, LVESVI: Left ventricle end-systolic volume index, EF: Ejection Fraction, CPB: Cardiopulmonary bypass.

surgery or PCI, and renal insufficiency. Preoperative physical examination, functional classification (NYHA), biochemical tests and transthoracic echocardiography (TTE) results were recorded. All patients were given beta-blockers, angiotensin-converting-enzyme inhibitor and statin during the follow-up, but none received spironolacton therapy in the postoperative period.

Patients were not allocated to any group preoperatively. Study was completed following the postoperative sixth-month control examination. Data were analyzed in two different topics according to; (a) LVRR occurrence and (b) EF change.

(a) LVRR Occurrence

As LVRR was calculated with both LVESD and LVESVI measurements, the number of patients allocated to each groups differed, based on the parameter used. Groups created with LVESD measurements were called as; group I (with LVRR) and group II (without LVRR). Groups created with LVESVI measurements were named as; group Ia (with LVRR) and group IIa (without LVRR).

(b) EF Change

LVEF was calculated with modified Simpson's rule: Left ventricular ejection fraction= [(end-diastolic-end-systolic)/end-diastolic] x 100(%).

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

A same cardiologist (IU) who was blind for study groups and design evaluated the patients for pre- and postoperative EF, LVESD and LVEDD, ventricular volumes in systole and diastole with TTE, and calculated the left ventricule end-systolic volume index (LVESVI). LVRR was considered significant if the decrease in LVESD was ³15% in the sixth month TTE control, compared to the initial echocardiographic measurements. Global left ventricular systolic function was assessed by the modified Simpson method using apical four-chamber view. Echocardiographic end-systolic and end-diastolic volumes were calculated by the same cardiologist using manual tracing with Siemens Acuson CV70 cardiovascular imaging system.

ANESTHETIC TECHNIQUE

Following premedication given 30 minutes before surgery (0.05 mg/ kg intramuscular midazolam), patients were admitted to the operating room and received 6 L/min oxygen via facemask. Monitoring consisted of ECG, invasive blood pressure, pulse oximetry, capnography, esophageal temperature, central venous and pulmonary artery pressures. Anesthesia was induced with lidocaine 1 mg/kg, midazolam 0.05 mg /kg, fentanyl 25-30 mcg/ kg, ketaminer (20:1 ratio vs dormicum), etomidate 0.2 mg/kg and pancuronium 0.1 mg /kg, and was maintained with propofol 0.05 mg/kg/min and remifentanil 25 mcg/kg/min infusions, and 2 mg of pancuronium administred every two hours.

SURGICAL TECHNIQUE

All operations were performed by the same surgical team. Following median sternotomy, all patients received left internal thoracic artery and saphenous vein grafts as conduits. Extracorporeal circulation was conducted at 32ºC with a membrane oxygenator (Dideco Compactflo EVO, Dideco, Sorin Group, USA) and a roller pump (Maquet Jostra HL20, Maquet, CA, USA). Proximal anastomoses were created under partial cross clamp during the re-warming phase. Operations were completed in the standard fashion.

SAMPLE COLLECTION

Plasma NT-proBNP, blood urea nitrogen and creatinine levels were studied from serial blood samples obtained from peripheral blood samples; (1) on the day before surgery, (2) on the third postoperative day and, (3) at the sixth postoperative month. For plasma NT-proBNP measurements, blood samples were obtained through an intravenous cannula that was placed 30 minutes before sampling, with the patient resting quietly while semi-recumbent position. Samples were collected in chilled Vaccutainers that contained ethylenediaminetetraacetic acid, placed on ice, and centrifuged 20 minutes at -4ºC. Plasma was stored at -80ºC until assay. Creatinine clearance was calculated for each patient.

MEASUREMENT OF NT-proBNP

Plasma NT-proBNP measurements were performed with IMMULITE 1000 TurboNT-proBNP which is a solid phase two site chemiluminescent immunometric assay kit (SIEMENS Healthcare Diagnostic Products Ltd. UK. Catalog#: LSKNT1, manufactured under license from ROCHE Diagnostic GmbH).

STATISTICAL ANALYSIS

Sample size was calculated with power analysis and no randomization method was used. In biostatistical analysis; data were presented as mean ± standard deviation. Paired t test was used for comparisons of preoperative and postoperative scores, student's t test (independent sample test) and Fisher's exact test were used for comparison of groups. Bonferroni test was performed as post-hoc test for pair -wise comparison of group differences. Kolmogorov-Smirnov test was applied to test for a normal distribution. Correlation calculations were done with Pearson test for data with normal distribution, and with Spearman test for data without normal distribution. P value was considered significant when <0.05. Statistical analysis was performed with SPSS 11.5 for Windows TM software (SPSS Inc., Chicago IL, USA).

RESULTS

LVESD data showed that, LVRR occurred in 17 patients (group I) but not in 23 (group II). Mean preoperative BNP value was 1119.83 ± 910.47 pg/ml in group I and 1341.67 ± 1548.78 pg/ml in group II (p= 0.574). Mean postoperative third day BNP value was 3912.35 ± 2051.51 pg/ml in group I, whereas 5821.39 ± 5631.50 pg/ml in group II (p= 0.145). The mean BNP value at the sixth postoperative month was 629.05 ± 526.30 pg/ml in group I and 1578.18 ± 1963.26 pg/ml in group II (p= 0.036). BNP value increased dramatically in the early postoperative phase, and decreased gradually in both groups. The mean BNP value at the sixth postoperative month was lower than the preoperative levels in group I (Figure 1). Change of BNP (ΔBNP) was calculated for both groups; 490.77 ± 630.90 pg/ml for group I and -236.50 ± 1097.05 pg/ml for group II. ΔBNP was found to be correlated with LVESD in group I (p= 0.012) but not in group II (p= 0.190).

BNP change was considered significant if ≥15% decrease occurred. In 18 patients BNP change was significant. Of these, 15 were as LVRR. Therefore, positive predictive value was 0.83 and negative predictive value was 0.91, sensitivity was 0.88, specificity 0.87, accuracy ratio was 0.87, and confidence interval (CI) was 95% (0.73-0.96).

LVESVI data showed that LVRR occurred in 20 patients (group Ia) but not in 20 patients (group IIa). The mean preoperative BNP value was 1244.00 ± 1093.70 pg/ml in group Ia and 1315.12 ± 1495.78 pg/ml in group IIa (p= 0.865). The mean BNP value on the third postoperative day was 4245.75 ± 2212.1 pg/ml in group Ia and 5774.35 ±

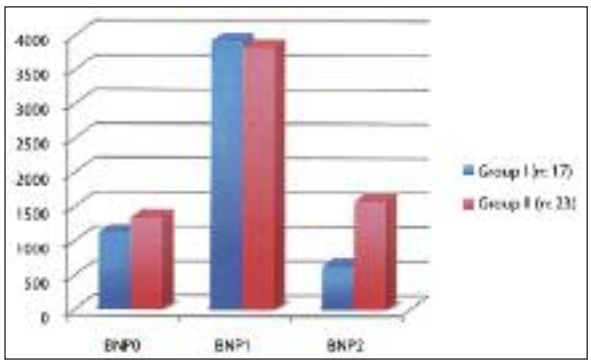

FIGURE 1: Diagram showing serum BNP levels of Group I and Group II. (Patients were grouped and named according to LVRR occurrence based on LVESD values.)

LVRR: Left ventricular reverse remodeling, LVESD: Left ventricle end-systolic dimension, BNP0: Preoperative BNP level, BNP1: BNP level on the third postoperative day, BNP2: BNP level at the sixth postoperative month.

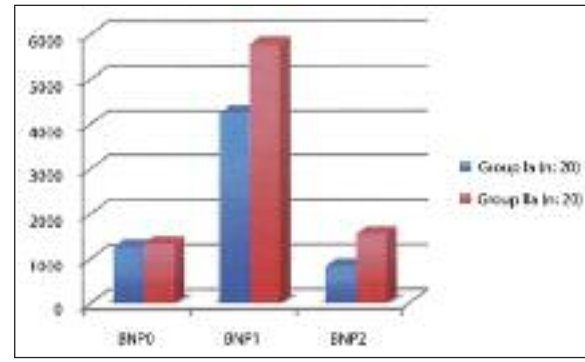

FIGURE 2: Diagram showing serum BNP levels of Group Ia and Group IIa. (Patients were grouped and named according to LVRR occurrence based on LVESVI values.)

LVRR: Left ventricular reverse remodeling, LVESVI: Left ventricle end-systolic volume index, ml/m², BNP0: Preoperative BNP level, BNP1: BNP level on the third postoperative day, BNP2: BNP level at the sixth postoperative month.

5852.46 pg/ml in group IIa (p= 0.161). The mean BNP value at the sixth postoperative month was 817.40 ± 749.64 pg/ml in group Ia and 1532.21 ± 2080.58 pg/ml in group IIa (p= 0.161) (Figure 2). Change of BNP (ΔBNP) was calculated for both groups; 426.60 ± 706.90 pg/ml for group Ia and -217.09 ± 1089.80 pg/ml for group IIa. ΔBNP did not correlate with LVESVI in group IIa (p= 0.384) but correlated with LVESVI in group Ia (p= 0.014).

In 21 patients BNP change was significant and of these, 16 were diagnosed as LVRR. Positive predictive value was 0.76, negative predictive value was 0.79, sensitivity was 0.80, specificity 0.75, and accuracy ratio was 0.77 with a CI of 95% (0.62-0.89).

EF Change

Left ventricular EF increased in 25 patients at the sixth postoperative month, decreased in 12 patients and did not change in three patients. The mean preoperative BNP levels (1279.5 ± 61293.85 pg/ml) correlated with preoperative and postoperative EF values (p= 0.037 and, p= 0.033, respectively). However, mean postoperative BNP levels (1177.30 ± 1515.67 pg/ml) correlated neither with the mean preoperative EF values (39% ± 5.9%) (p= 0.234), nor the mean postoperative EF values (43% ± 9.7%) (p= 0.085).

DISCUSSION

Ventricular remodeling (VR) that occurs after myocardial infarction consists of adaptive and maladaptive responses to changes in hemodynamics, as less myocardium attempts to maintain the same cardiac output. These responses include cardiac dilatation and hypertrophy, scar formation, neurohormonal changes, cytokine activation and oxidative stress.[21] Cardiac fibroblasts (CF), histologically key component of VR, which compose 60-70% of the heart, also regulate myocardial structure, organize mechanical, chemical, and electrical signals between cellular and non-cellular cardiac components. In the post infarction process, CF become highly proliferative even invasive, and remodel the cardiac interstitium by increasing secretion of extracellular matrix (ECM) degrading metalloproteinase and increasing collagen turnover. Although these changes serve initially as an important reparative wound healing response, in the longer term they become maladaptive leading to collagen accumulation, cardiac fibrosis, and finally loss of cardiac function. Natriuretic peptides work against this maladaptive process. Recent studies suggest that the intracardiac natriuretic peptides/cGMP system plays a counter-regulatory role against the intracardiac renin-angiotensin-aldosterone system and TGF-beta mediated pathway, and thus protects the heart against remodeling.[24,25] Clinically, natriuretic peptides and CF interaction results as 'remodeling' or 'reverse remodeling'. This interaction constituting the molecular basis of remodeling, explains the strong correlation between left ventricle size and BNP levels clearly shown by our data.

Left ventricular remodeling is generally a poor prognostic sign and is strongly associated with cardiac failure. Patients with LV remodeling have a higher risk for cardiovascular morbidity and mortality.[26] Therefore, prevention of LV remodeling is crucial for survival. The treatment options for prevention of left ventricle dilatation or remodeling include medical treatment, percutaneous coronary intervention, and coronary surgery with or without surgical ventricular restoration. The open artery hypothesis declared that, restoration of antegrade blood flow to the peri-infarct area is beneficial to the myocardium even late to prevent myocardial necrosis.[27] A possible mechanism for the explanation of late reperfusion advantage may be 'apoptosis inhibition' which is responsible for the late phase of remodeling.[28] Natriuretic peptides block the apoptosis process and thus cease late remodeling progression. Wu et al showed that BNP-mediated attenuation of apoptosis was associated with increased expression of an anti-apoptotic protein Bcl-2 and reduced expression of a pro-apoptotic protein Bax.[29] BNP can be considered as an anti-remodeling peptide and serum BNP levels should be directly proportional with the remodeling process and LVESVI.

In this study we planned to show that; (1) BNP is a marker of LV reverse remodeling which was documented with various studies in different patient groups (especially in patients with valvular he-

art disease and dilated cardiomyopathy) (2) a low BNP value reflects good outcome following CABG in patients with myocardial infarction. The relationship of BNP and remodeling was previously documented by numerous studies in patients underwent PCI following MI.[30,31] Brugada et al. noted prevention of LV remodeling after MI can be achieved with early PCI in 62% of patients and BNP value at admission and follow-up can predict LV dilatation.[31] Similarly, numerous studies were published reporting a correlation between BNP levels and LV function or outcome following CABG.[4,8,10,18,22,32-71] The effects of coronary bypass on ventricle diameters and shape have not been well-documented with large studies. Surgical Treatment for Ischemic Heart Failure (STICH) investigators reported 6% reduction in left ventricular end systolic volume index at the fourth postoperative month following CABG in patients with ischemic cardiomyopathy.[49] Similarly, we found 6.7% mean reduction in the LVESVI at the sixth postoperative month (48.65 ± 3.04 vs. 45.37 ± 3.23). LVESVI decreased in 27 of 40 patients, in other words, LV remodeling was prevented in 67.5% of patients with CABG. In group Ia, LVESVI decreased 10.80 ml/m^2, but in group IIa it increased 4.20 ml/m^2. ΔBNP was correlated with LVESVI in group Ia.

Briefly; (1) CABG prevents the LV remodeling following myocardial infarction, (2) BNP changes are directly proportional with LVESVI and thus can predict and reflect success of the revascularization procedure.

Anticipating the correlation of LVEF and BNP change is not surprising, since LVEF calculation relies on ventricular volumes and a strong association between ventricle size and BNP was well documented.[5,7,12,31,50,51] Ejection fraction is considered as a powerful indicator of operative outcomes by most of the surgeons, and recent studies investigating predictive value of BNP, Euroscore and LVEF showed similar results.[36,40] The utility of natriuretic peptides levels to optimize operation time after myocardial infarction should be investigated.

Evidence indicates that a reverse remodeling effect achieved by cardiac surgery may be mirrored by a reduction in BNP release. Further studies are needed to define the role of NT-proBNP determination in assessing the long-term prognosis of patients receiving cardiac surgery.[43]

In conclusion; BNP reflects left ventricular reverse remodeling and function after coronary artery bypass surgery in patients who had myocardial infarction.

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