Comparison of the NT-proBNP levels between coronary artery bypass grafting patients and concomitant coronary artery bypass grafting with valve replacement patients

Koroner arter bypass greftleme ve koroner arter bypass greftleme ile birlikte kapak değişimi yapılan hastalarda NT-proBNP düzeylerinin karşılaştırılması

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Background: In this article, we examined the relationship between the pre- and postoperative brain natriuretic peptide (BNP) levels and pre-, intra-, and postoperative hemodynamic parameters in patients undergoing coronary artery bypass grafting (CABG) and combined CABG and valve operations.

Methods: Thirty patients with II and III ASA enrolled in the study were divided into two groups, each with 15 patients: CABG surgery (Group 1, 13 males, 2 females; mean age 62.2±8.6 years) and CABG + valve replacement surgery (Group 2, 13 males, 2 females; mean age 64.1±10.6 years). Patient data were prospectively collected. Anesthetic induction and endotracheal intubation were performed with 10 μg/kg fentanyl and 0.1-0.2 mg/kg etomidate, and 0.15 mg/kg cisatracurium. Isoflurane 1%, cisatracurium 0.1 mg/kg/hr infusion and 0.15 μg/kg/min fentanyl was used for anesthetic maintenance. Systemic and pulmonary arterial pressures were monitored. NT-proBNP levels and troponin T and CK-MB levels were recorded at pre- and postoperative 4th and 12th hours in both groups.

Results: Demographic and hemodynamic data were not significantly different between the two groups. In both groups, NT-proBNP values increased to peak levels at 24 hours postoperatively, however it was not associated with hemodynamic parameters and inotropic support.

Conclusion: There was no statistical difference between NT-proBNP levels in both groups preoperatively. Postoperative NT-proBNP levels were higher in group 2 (longer cross-clamp, and cardiopulmonary bypass time) at the 4th and 12th hours. However the duration in hospital and in the intensive care unit were longer in group 1 patients with high preoperative NT pro-BNP levels.

Key words: Brain natriuretic peptide; coronary artery bypass grafting; endocrine system.

Amaç: Bu çalışmada koroner arter bypass greft (KABG) ve KABG ile birlikte kapak cerrahisi uygulanan hastalarda ameliyat öncesi ve sonrası beyin natriüretik peptid (BNP) düzeylerinin, ameliyat öncesi, sırası ve sonrası hemodinamik parametrelerle olan ilişkisi araştırıldı.

Çalışma planı: Çalışmaya alınan ASA II ve III olan 30 hasta, KABG (Grup 1; 13 erkek, 2 kadın; ort. yaş 62.2±8.6 yıl) ve KABG + kapak değişimi (Grup 2; 12 erkek, 3 kadın; ort. yaş 64.16±10.6 yıl) uygulanacak şekilde 15'er kişilik iki gruba ayrıldı. Hasta verileri ileriye dönük olarak toplandı. Hastalara, 10 μg/kg fentanil ve 0.1-0.2 mg/kg etomidat, 0.15 mg/kg sisatrakuryum verilerek anestezi indüksiyonu ve endotrakeal entübasyon yapıldı. Anestezik idamede izofluran %1, sisatrakuryum 0.1 mg/kg/saat infüzyon ve 0.15 μg/kg/dk fentanil kullanıldı. Sistemik ve pulmoner arteryel basınçları izlendi. Her iki grupta da, NT-proBNP düzeyleri ve troponin T ve CK-MB düzeyleri ameliyat öncesi ve sonrası 4. ve 12. saatlerde kaydedildi.

Bulgular: İki grup arasındaki demografik ve hemodinamik verilerde anlamlı farklılık bulunmadı. Her iki grupta da NT-proBNP, ameliyat sonrası 24. saatte zirve seviyeye ulaşmasına rağmen, hemodinamik parametreler ve inotropik destekle ilişkili değildi.

Sonuç: Ameliyat öncesi her iki grupta da NT-proBNP düzeyleri arasında istatistiksel fark yoktu. Kros-klemp ve kardiyopulmoner bypass süresi uzun olan grup 2'de NT-proBNP seviyeleri ameliyat sonrası 4. ve 24. saatlerde daha yüksekti. Ayrıca ameliyat öncesi NT-proBNP seviyeleri yüksek düzeyde olan grup 1'deki hastaların, yoğun bakım ünitesi ve hastanede kalış süreleri daha uzun idi.

Anahtar sözcükler: Beyin natriüretik peptid; koroner arter bypass greftleme; endokrin sistem.

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Electrocardiography (ECG), hemodynamic parameters, biochemical markers like creatinin kinase (CK), myoglobulin creatinin kinase (CK-MB) and troponins and transesophageal echocardiography (TEE) are widely used in the diagnosis of perioperative myocardial infarction and cardiac failure during coronary cardiac surgery.[1,2]

Recently, brain natriuretic peptide (BNP) secretion levels due to the increased left ventricle volume and pressure have been used in the early diagnosis and treatment of myocardial damage and cardiac failure after cardiac operations.[3-6]

Investigations with BNP level are focused on the early determination of complications like myocardial infarction and cardiac failure due to the ischemia caused by prolonged cross-clamp time in coronary cardiac operations. Increase in BNP is not only determined in prolonged ischemic time complications but is also true for patients with asymptomatic left ventricle dysfunction and also may be in correlation with the patient's functional capacity and prognosis.[7-9]

Publications show the value of the correlation between BNP and proBNP levels and the early determination and treatment of the cardiac complications during cardiac surgery in coronary artery patients. They all agree that those complications have often been seen with the myocardial damage in complex surgical patients with prolonged cross-clamp time. But we have not found any study on patients who underwent combined coronary and valve surgery. Our aim was to determinate the correlation of the hemodynamic parameters and the BNP levels correlation in the pre- and postoperative period in these patients.

PATIENTS AND METHODS

Thirty patients with II and III ASA physical score were admitted to the research. Patients were selected randomly and grouped into elective coronary artery bypass grafting (CABG), (Group 1; 13 males, 2 females; mean age 62.2±8.6 years) and concomitant CABG + valve replacement surgery (Group 2; 13 males, 2 females; mean age 64.1±10.6 years). Patients with unstable angina, left bundle branch block, pacing devices, unstable hemodynamics, organ transplant, acute myocardial infarcts, acute cardiac failure, preoperatively requiring inotropics, pulmonary embolism, renal insufficiency, hepatic cirrhosis and emergency status were excluded.

All patients were visited the day before the operation and informed consent was asked for. All patients were premedicated with 10 mg diazepam in the evening before the operation. On the morning of the operation, they were sedated with 0.05 mg midazolam in the operating room before monitoring and catheterization. Patients were monitored with five lead ECG, noninvasive blood pressure device, and peripheral oxygen saturation (SpO_2) probe.

Patients inhaled 2 lt/min, O_2 with nasal canulae and canullated in the antecubital veins with 16 G, radial artery with 20 G and right internal jugular vein with 7.5 F intraducers and pulmonary thermodilution catheter (Edwards Lifesciences 7.5 F, Irvine, CA, USA) for continuous cardiac output monitorization, before anesthetic induction with local anesthesia.

Heart rate (HR), systolic, mean diastolic blood pressures, central venous pressure (CVP), pulmonary venous pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), body heat, SpO_2, and blood gas measurements were determined before anesthetic induction, at the fifth min of intubation, just before incision time, after sternotomy, before and after cardiopulmonary bypass (CPB), at postoperative 1st, 4th, 12th hours; after extubation, and the 24th hour.

All patients were ventilated with 100 O_2 three minutes before induction and the anesthetic induction was started with 10 μg/kg fentanyl and 0.1-0.2 mg/kg ethomidate and intubated with 0.15 mg/kg cis-atracurium injection. Isoflurane 1%, and cis-atracurium 0.1% mg/kg/hr infusion and fentanyl 0.15 μg/kg/min were used for anesthetic maintenance.

N-terminal (NT) proBNP measurements were done from blood samples taken just before anesthetic induction, and postoperative 4th and 24th hours. Troponin T, CK-MB, NT-proBNP tests were done with Roche Elecsys 2010 (Roche Elecsys 2010, Indianapolis, USA) with electro-immunoassay processor.

0.1 μg/kg/min cis-atracurium and 0.15 μg/kg/min fentanyl infusion started after the anesthetic induction. Mechanical ventilation was done with 50% O_2 and air.

Starting with 3 mg/kg heparin administration, the activated coagulation time was regulated between 450-600 seconds. After endotracheal intubation cardiopulmonary circulation was started. Operations were done with mild hypothermia (28-32 ºC) and hemodilution (Hct, 25-30%) and the arterial oxygen pressure (AOP) maintained between 50-80 mmHg and the pump flow rate was at minimum 2 lt/m^2.

After releasing the aortic cross-clamp, patients were ventilated with oxygen. With the completion of the operative procedures, normothermia was obtained and the precise preload regulated with the pump prime before termination of the extracorporeal circulation. To maintain Hct at 30%, blood or crystalloid was infused if required. Medications were restarted. Total pump time, aortic cross-clamp time and operative times were registered.

Table 1. Patient demographic and peroperative data

	Group 1	Group 2
	Mean±SD	Mean±SD
Age (year)	62.2±8.6	64.1±10.6
Height (cm)	167.9±6.3	170.1±7.5
Weight (kg)	77.7±10.1	76.8±13.9
Body surface area (m^2)	1.9±0.1	1.9±0.2
Ejection fraction %	60.2±8.2	54.2±13.0
The number of grafted vessel	2.7±0.6*	1.7±0.8
Perfusion time (mn)	125.7±45.6	161.7±59.3
Duration of anesthesia (min)	302.1±63.8	334.9±113.2
Duration of operation (min)	277.3±65.8	308.0±111.7
Duration of cross-clamp (mn)	60.9±18.3	103.6±25.9*

Values are mean scores ± standart deviation (SD); *: Means statisticaly significant (p<0.05).

Patients were transported to the ICU with ventilator support and in monitored status.

Heart rate, arterial blood pressure (ABP), CVP, body heat, SpO2, blood gas measurements, CO measurements of the patients were registered at postoperative 1st, 4th, 12th, and 24th hours. Extubation time, spending time both in the ICU and at the hospital were also registered.

Statistical analysis

Statistical Package for social sciences (SPSS) for Windows 10.0 statistical package (SPSS Inc., Chicago, Illinois, USA) was used for analyses. Comparisons were done with Student's t-test and Mann-Whitney U-test. Correlating analysis was done with the Pearson test. A p<0.05 was considered significant. Analysis of variance (ANOVA) was used to test for repeated measurements.

RESULTS

There was no significant statistical difference between two groups regarding age, weight, height, body surface area (BSA) and ejection fraction (EF) data preoperatively (p>0.05; Table 1). There was no significant statistical difference between two groups regarding anesthesia time, total pump time and operation time data (p>0.05). But the aortic cross-clamp time was longer in group 2 and the number of vessels grafted was much higher in group 1 and was found statistically significant (p<0.05; Table 1).

Hemodynamic data

Heart rate: Patients' HR data are shown in table 2. There was no statistically significant difference between two groups (p>0.05).

Table 2. Hemodynamic changes

	Preoperatif	After induction	After sternotomi	Before bypass grafting	After bypass	At the end of surgery	Postoperatif 4th hour	Postoperatif 24th hour
HR (beats/min)								
Group 1	71.8±22.9	64.6±10.9	73.1±11.4	83.5±17.9	89.2±20.4	90.8±16.1	96.9±13.9	97.5±10.3
Group 2	76.3±15.4	70.9±18.7	86.2±31.6	83.2±24.2	93.9±18.9	96.0±18.9	101.7±10.2	93.8±16.7
SAP (mmHg)								
Group 1	138.4±29.1	136.1±21.7	127.6±16.0*	103.6±16.4	105.6±14.3	104.3±11.0	105.1±12.7	113.8±10.3
Group 2	132.7±27.5	106.9±29.6	111.8±22.5	96.9±13.4	101.9±11.9	101.7±10.4	102.7±15.0	105.5±14.5
MPAP (mmHg)								
Group 1	8.3±3.0	10.2±3.3	8.8±5.6	6.1±2.7	6.3±4.2	7.2±3.9	10.7±2.6	10.3±3.7
Group 2	14.4±10.1*	16.3±9.8*	10.5±9.6	8.9±6.6*	12.4±7.5*	10.1±5.7*	11.4±5.1	16.3±17.5
PCWP (mmHg)								
Group 1	4.4±2.5	8.8±3.4	5.7±3.6	3.7±3.5	3.4±2.8	5.6±3.5	8.9±3.1	9.4±3.6
Group 2	6.7±9.1*	10.8±7.5*	6.5±7.7	5.5±5.1*	8.3±6.7	8.4±6.7	8.8±4.4	8.3±4.6
CVP (mmHg)								
Group 1	4.4±2.5	8.8±3.4	5.7±3.6	3.7±3.5	3.4±2.8	5.6±3.5	8.9±3.1	9.4±3.6
Group 2	6.7±9.1	10.8±7.5	6.5±7.7	5.5±5.1	8.3±6.7*	8.4±6.7	8.8±4.4	8.3±4.6
CO (L/min)								
Group 1	5.8±1.6	5.5±1.3	8.8±5.6	3.4±1.2	5.5±2.7	4.7±1.1	5.3±2.4	5.9±1.5
Group 2	5.2±2.0	5.1±1.7	3.8±1.2	3.3±1.2	4.4±1.4	5.4±1.7	4.4±1.6	5.4±1.7

Values are mean scores ± standart deviation; *: Means statisticaly significant (p<0.05); HR: Heart rate; SAP: Systolic arterial pressure; MPAP: Mean pulmonary arterial pressure; PCWP: Pulmonary capillary wedge pressure; CVP: Central venous pressure; CO: Cardiac output.

Heart rate data in group 1 was significantly higher in all the postoperative measurements than the preoperative period (p<0.05).

Systolic arterial pressure (SAP): Data of SAP are shown in table 2. After sternotomy SAP values were higher in group 1 than group 2 and were found statistically significant (p<0,05).

Central venous pressure (CVP): Central venous pressure data are shown in table 2. Only the post-bypass CVP values were higher in group 2 than group 1 (p<0.05).

Pulmonary arterial pressure (PAP): Pulmonary arterial pressure data are shown in table 2. In group 2 preoperative values and values at the time of anesthetic induction, at the post 5th min of intubation, at the termination of anesthetic induction, at the pre-incision time, at the pre- and post-bypass period and at the postoperative 1st hour were significantly higher than group 1.

Pulmonary capillary wedge pressure (PCWP): Data of PACWP are shown in table 2. Preoperative, post induction period and post pump period PCWP values were higher in group 2 than in group 1 and were statistically significant (p<0.05).

Cardiac output (CO): Data are shown on the table 2. Cardiac output values were similar in both groups (p>0.05).

NT-proBNP levels: All the data obtained at the preoperative period and at the postoperative 4th and 24th hours levels are shown in figure 1.

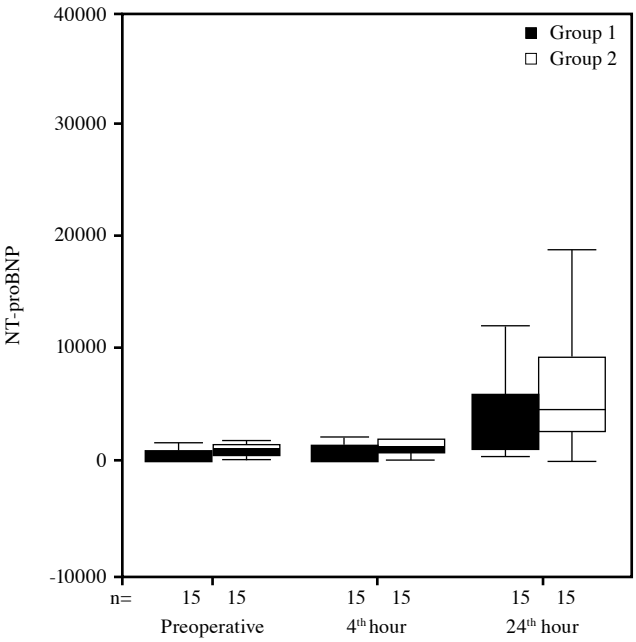

Fig. 1. N-terminal prohormone brain natriuretic peptide levels.

At the preoperative period NT-proBNP levels of the seven patients (40.6%) were below normal limits (125 pg/ml). In the rest of the patients (59.4%) NT-proBNP levels were higher than normal limits. Preoperative NT-proBNP levels of all the patients of group 2 were higher than 125 pg/ml.

In group 1, postoperative mean NT-proBNP level at the 4th hour was 1287, 8±239.6 pg/ml and the 24th hour mean NT-proBNP level was 5736, 0±777.2 pg/ml. Those levels were found to be much higher than preoperative levels and the correlation was positive in statistical analyses (p<0.05), but the rise in postoperative mean levels of both groups was not statistically significant.

In group 1, at the postoperative 24th hours, there was a statistically negative correlation between EF values and NT-proBNP levels (p<0.05). There was also a statistically significant correlation between cross-clamp time and NT-proBNP levels (p<0.05).

Naturally, cross-clamp time in group 2 was longer than group 1 and the difference between the two groups was statistically significant (p<0.05).

Recently, preoperative PAP values and NT-proBNP values correlations have been published.[10] Our findings showed the same correlations. Using Pearson correlation test, pre- and postoperative 4th hour PAP and NT-proBNP values correlation was found statistically significant (p<0.05 for group 1 and, p<0.01 for group 2).

There was a statistically significant correlation between preoperative PAP and NT-proBNP levels (p<0.05).

At the postoperative fourth measurements, there was statistically significant correlation only in group 2 (p<0.05).

Troponin T and CK-MB levels: Data are shown in table 3. There was no statistically significant correlation at the preoperative period in troponin T levels between two groups (p>0.05). At the postoperative period, troponin T levels were much higher in group 2 and was statistically significant (p<0,05).

Morbidity and mortality: During the ICU period, one patient in group 2 had an attack of ventricular fibrillation on the second postoperative day. One patient in

Table 3. Troponin T and CK-MB levels

	Group 1	Group 2
	Mean±SD	Mean±SD
Pre Tr T	0.03±0.05	0.03±0.03
Post Tr T	0.59±065	0.82±0.81
Pre CK-MB	2.99±1.56	3.31±1.40
Post CK-MB	20.20±7.05	35.58±16.98*

Values are mean scores ± standart deviation (SD); *: Means statisticaly significant (p<0.05); CK-MB: Creatine kinase isoenzyme in myocardium.

Table 4. Patient hospital stay, ICU time and mortality

	Group 1			Group 2		
	n	%	Mean±SD	n	%	Mean±SD
ICU stay (day)			3.1±1.4			5.8±7.4
Hospital stay (day)			10.0±5.5			9.7±7.5
Mortality	1	10.6		2	13.3	

Values are mean scores ± standart deviation (SD); *: Means statisticaly significant ($p<0.05$); ICU: Intensive care unit.

group 1 who needed intra aortic balloon support during the postoperative period was rehospitalized on the 8th day after discharge due to pleural effusion. One patient in group 2 was rehospitalized on the 7th day after discharge due to atrial fibrillation with rapid ventricular response. There was statistically significant correlation between hospital stay and NT-proBNP levels ($p<0.05$).

Two patients who underwent CABG + aortic valve replacement (AVR) in group 2 died. One patient in group 1 died due to gastrointestinal complication.

DISCUSSION

Brain natriuretic peptide secretion due to the left ventricular pressure load and wall stretch has been recently used in the early diagnosis of cardiac failure and myocardial damage.[3-6] Atrial natriuretic peptide (ANP) and BNP level alterations due to the perioperative acute myocardial ischemia and necrosis during cardiac surgery with patients receiving CABG and concomitant CABG and valve surgery and their value in prognosis has been the subject of a lot of publications.[7,11-13] Common findings in all publications are that the rise in BNP levels and cross-clamp durations are in correlation.[13]

Diminished left ventricular compliance and contractile dysfunction due to myocardial ischemia causes rises in left ventricular end-diastolic and atrial pressures and results in secretion of the natriuretic peptides during CABG surgery.[5-8,11]

In the case of chronic mitral regurgitation and aortic stenosis myocardial decompensation results from different mechanisms and in both conditions it results in ventricular failure. It is known that the more stenotic a valve, the greater the rise of the BNP level.[4]

Brain natriuretic peptide secretion as a response of ventricular wall stretch, secreted from cardiac ventricles is a good parameter for demonstration of cardiac overload. Secreted BNP from stretched myocardium will be derived in NT-proBNP and BNP structures in the circulating blood.

The active and more effective format is BNP. Since eradication of the BNP from circulating blood is more rapid, it is safer to measure the NT-proBNP level. Also the half life and constant secretion of the NT-proBNP make it a preferred parameter for many centers.

Some investigations are focused on the correlation between valvular disease like aortic stenosis and mitral regurgitation and the BNP or NT-proBNP levels. The result is that the concentration of the plasma BNP is a noninvasive parameter for evaluation of disease progress and the prognosis of the ventricular function loss.[12]

Berendes et al.[6] investigated BNP concentrations in patients receiving CABG, aortic valve, and mitral valve operations. Brain natriuretic peptide concentrations in the preoperative period in patients with valve operations were within normal limits, but the concentration was found high in CABG patients. They showed direct correlations between prolonged cross-clamp time and higher BNP concentration and also the effect of higher preoperative BNP concentrations on higher postoperative mortality. They declared that depending on cross-clamp time, myocardial ischemia and prolonged left ventricular higher pressure and preload results with higher BNP secretion may be a remark for patients with preoperative high BNP concentrations in the postoperative early period.[7]

Like Berendes et al.[6] we also found high NT-proBNP concentrations in patients who underwent concomitant CABG and valve replacement (Group 2), due to the longer cross-clamp time. But the difference was not statistically significant between two groups ($p>0.05$). The highest BNP concentration was found at the 24th hour measurement in a patient who underwent CPB twice in group 2.

Weber et al.[4] demonstrated that high NT-proBNP concentrations in aortic valve disease correlated with the severity of the pathology and NT-proBNP concentration falls with the surgical treatment of the disease. In patients who were treated conservatively, the NT-proBNP concentrations were higher as the disease progressed. They stated that in evaluating the myocardial stress and monitoring the aortic valve disease prognosis NT-proBNP concentrations may be used as a biochemical marker.

We found higher BNP concentrations preoperatively in group 2. The ICU stay and hospitalization of the

patients were longer and mortality rate was higher in this group although there was no statistically significant difference. Despite the small number of patients, we observed that preoperative elevated BNP concentrations may be a higher risk factor for cardiac surgery.

Saribulbul et al.[14] demonstrated in their study that there were significant correlations between preoperative BNP concentrations, cross-clamp time and the use of inotropics. They found higher cross-clamp time in patients with preoperative high BNP levels.

The highest BNP concentration was found at the 24th hour and sustains seven days postoperatively.[5,6] In group 2 who underwent concomitant operations, two patients underwent mitral valve replacement and 13 patients underwent AVR. NT-proBNP levels in both groups were higher in group 2; however it was not statistically significant ($p>0.05$).

Although there was no significant difference in hospital stay and ICU in groups 1 and 2, ICU stay was a bit longer in group 2.

NT-proBNP concentrations may be used preoperatively as a risk factor parameter and may be a monitoring marker at the postoperative early period and also a prognostic indicator in cardiac surgery.

Declaration of conflicting interests

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