CLINICS

CLINICAL SCIENCE

Assessment of the left atrial volume index and plasma NT-proANP level in patients with acute ST-elevation myocardial infarction

Ahmet Bacaksiz,[I] Mehmet Akif Vatankulu,[I] Mehmet Kayrak,[II] Hasan Huseyin Telli,[II] Selim S. Ayhan,[III] Osman Sonmez,[I] Ayse Alp,[IV] Sadik Buyukbas[V]

[I] Bezmialem Foundation University, Faculty of Medicine, Department of Cardiology, Istanbul/Turkey. [II] Konya Necmettin Erbakan University, Meram School of Medicine, Department of Cardiology, Konya/Turkey. [III] Abant Izzet Baysal University School of Medicine, Cardiology, Bolu/Turkey. [IV] Diyarbakir Training and Research Hospital, Department of Biochemistry, Diyarbakir/Turkey. [V] Mustafa Kemal University, School of Medicine, Department of Biochemistry, Hatay/Turkey.

OBJECTIVES: Acute ST-elevation myocardial infarction is associated with ventricular dysfunction due to ischemia-induced progressive myocardial damage. The decrease in ventricular compliance causes left atrial dilatation and stretching of the atrial myocardium, which are the main stimuli for the secretion of atrial natriuretic peptide. The aim of this study was to evaluate left atrial dimensions and atrial natriuretic peptide levels in patients early after their first acute ST-elevation myocardial infarction and assess the probable interaction between coronary lesions and these measurements.

METHODS: A total of 110 patients with acute myocardial infarction and 50 controls were studied. Plasma atrial natriuretic peptide was measured at admission. Left ventricular function, diameter, and volume index were evaluated using transthoracic echocardiography. Gensini and vessel scores of the patients who underwent coronary angiography were calculated.

RESULTS: Plasma atrial natriuretic peptide in the patients with myocardial infarction was increased compared with that in controls (3.90 ± 3.75 *vs.* 1.35 ± 0.72 nmol/L, $p<0.001$). Although the left atrial diameter was comparable in patients and controls, the left atrial volume index was increased in patients with acute myocardial infarction (26.5 ± 7.1 *vs.* 21.3 ± 4.9 mL/m^2, $p<0.01$). Multivariate regression analysis showed a strong independent correlation between the left atrial volume index and the plasma atrial natriuretic peptide level ($\beta = 0.23$, $p = 0.03$).

CONCLUSIONS: The left atrial volume index and plasma atrial natriuretic peptide level were correlated in patients with acute myocardial infarction.

KEYWORDS: Myocardial Infarction; Atrial Natriuretic Peptide; Heart Atria.

Bacaksiz A, Vatankulu MA, Kayrak M, Telli HH, Ayhan SS, Sonmez O, et al. Assessment of the left atrial volume index and plasma NT-proANP level in patients with acute ST-elevation myocardial infarction. Clinics. 2013;68(7):997-1003.

Receveid for publication on January 11, 2013; **First review completed on** March 12, 2013; **Accepted for publication on** March 30, 2013

E-mail: ahmetbacaxiz@yandex.com

Tel.: +90 212 453 1700-1691

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of both morbidity and mortality worldwide (1). It encompasses a wide clinical spectrum ranging from silent ischemia to sudden death. Within this spectrum, acute ST-segment elevation myocardial infarction (STEMI) is the most significant form of the disease with respect to its diagnosis, treatment, and prognosis. Various degrees of left ventricular systolic and diastolic dysfunction occur during STEMI (2). Several parameters are used for the determination of left ventricular (LV) diastolic function, but most of them are affected by a number of technical and physiological factors, including heart rate, age, cardiac rhythm, preload, afterload, and LV geometry (3).

The atria are cardiac structures that are often overlooked during a routine echocardiographic examination (4). In general, the measurement of left atrial antero-posterior diameter (LAAPD) with M-mode echocardiography is considered sufficient. Although this method is simple, its accuracy in reflecting LA size is controversial due to the asymmetric structure of the LA. Volume calculation represents LA size more consistently than diameter or area measurements. The LA volume indexed to body surface area (LAVI) is the recommended method for LA size

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2013(07)18

quantification (5). Increased LA volume is a strong predictor of mortality after STEMI and provides superior prognostic information compared with conventional LV systolic and diastolic function measurements and clinical data (6).

The natriuretic peptides comprise several structurally related molecules, such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which play important roles in cardiovascular homeostasis (7). ANP is secreted from atria as a response to increased intra-atrial pressure and is eliminated from the circulation in minutes either enzymatically or through the clearance receptor (8). The biologically inactive N-terminal peptide of pro-atrial natriuretic peptide (NT-proANP) is secreted into plasma in equimolar amounts as ANP, but it has a higher plasma concentration than ANP due to decreased degradation in vivo, which makes it a more appropiate biomarker (9). Plasma ANP is increased in STEMI due to LV load and myocardial damage (10,11). In patients with STEMI, the plasma ANP level helps predict the prognosis and identify high-risk patients (12). Svanegaard et al. demonstrated that the distension of the LA, rather than the dilatation of the LV, is related to the concentration of ANP (13). To our knowledge, no study has investigated the association between LAVI and plasma ANP level during STEMI. The purpose of this study was to evaluate LAVI and ANP in patients with STEMI.

MATERIALS AND METHODS

Patients

This prospective study enrolled 110 patients with a STEMI diagnosis. A diagnosis of acute STEMI was made based on the current criteria (14). Additionally, 50 age- and gender-matched subjects with complaints of exercise angina who underwent elective coronary angiography that revealed normal coronary arteries were used as the control group.

The following were exclusion criteria because of the influence of each condition on echocardiographic variables or the ANP level: a) patients admitted to a hospital more than 12 hours after the onset of symptoms; b) patients who presented with a heart rhythm other than sinus rhythm; c) patients whose echogenicity was insufficient for transthoracic echocardiographic examination; d) patients with atrial infarction (elevated PR segment at leads I, II, III, V5, and V6; 0.15-mV depression at precordial leads; or 0.12-mV depression at leads I, II, and III); e) patients with Killip class $\geq$III heart failure or cardiogenic shock; f) patients with renal failure (serum creatinine $\geq$1.5 mg/dL), chronic pulmonary or hepatic disease, or cancer; g) patients with an acute infection, severe trauma, surgical operation or burns within the last month; h) patients with a history of prior MI, percutaneous coronary intervention (PCI), or coronary artery by-pass graft operation; i) and patients with cardiomyopathy or moderate to severe valvular heart disease. Only patients with Thrombolysis in Myocardial Infarction grade 3 flow in the infarct-related artery (IRA) after PCI and patients with $\geq$50% ST resolution at 90 minutes after fibrinolysis were included in the study to eliminate the possible effects of inadequate reperfusion.

Age, gender, height, weight, waist and hip circumferences, and atherosclerotic risk factors were recorded for all patients. Body mass index (BMI) and body surface area (BSA) were calculated. Pulse and blood pressure were measured at the time of presentation. All patients were informed about the nature and purpose of the study, which was approved by the local ethics committee.

Echocardiographic evaluation

All patients were evaluated by two-dimensional pulsed-wave Doppler and pulsed-wave tissue Doppler echocardiography. The electrocardiogram-guided echocardiographic examination conducted using a transthoracic approach was performed by an experienced sonographer who was blinded to the study, with the patient in the left lateral decubitus position within 48 hours after admission, by using Philips ATL HDI 5000 (Philips Medical Systems, Advanced Technology Laboratories, Bothell, Washington, USA) and Philips Envisor C HD (Philips Medical Systems, Andover, MA, USA) echocardiography devices and 2–4-MHz phase transducers. All measurements were obtained as per the criteria recommended by the American Echocardiography Society (5). The left atrial antero-posterior diameter (LAAPD) and septal wall thickness were obtained from standard parasternal long-axis images. Left ventricular end-systolic (LVESD) and end-diastolic diameter (LVEDD) and ejection fraction (EF) from apical four- and two-chamber views were measured by using the modified Simpson method (15). Transmitral flow samples were obtained by pulsed-wave (PW) Doppler such that apical four-chamber views were parallel to the blood flow with the sample volume located at the level of the mitral leaflet tips. From the recordings, peak early (E) and late (A) transmitral filling velocities, isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and ejection time (ET) were measured, and the LV myocardial performance index (MPI) was calculated.

The maximal LA volume was measured from the apical four-chamber view by using the modified Simpson method in end-systole before mitral valve opening. The LAVI was obtained for all patients by dividing the LA volume by the BSA. Additionally, early diastolic velocity (Em) was measured using the tissue Doppler function of the same devices, with the sample volume from the apical four-chamber view located at the septal edge of the mitral annulus. The average value of three consecutive heart beats was obtained at the end of exhalation.

To assess the intra-observer variability, echocardiographic measurements were repeated in ten subjects the next day by the same investigator. To assess the inter-observer variability, transthoracic echocardiography was performed by a second observer on the same ten patients after the first echocardiography. The intra- and inter-observer variability of LA volume were 7.5 ± 6.1 and 9.3 ± 7.2 mL, respectively, indicating good agreement.

Coronary angiography

Coronary angiography was performed using a monoplane cine-angiography system (Philips Optimus 200 DCA and Integris Allura 9 angiography devices; Philips Medical Systems, Eindhoven, Netherlands). Selective coronary angiography was performed at standard positions by the Judkins technique and a right and left transfemoral approach. Iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as opaque material. Angiographies were recorded at 25 frames/second by using 35-mm cinefilm. The Gensini score and vessel score were used to determine the severity and the extent of atherosclerotic

CAD, respectively (16,17). For coronary artery scoring, one point was assigned to each artery when there was 70% or more stenosis in the three main coronary arteries and their major side branches. One additional point was assigned when there was 50% or greater stenosis in the left main coronary artery (LMCA), with a maximum total score of 4. The Gensini score was obtained by considering the severity of lesions at certain segments of the LMCA, left anterior descending artery (LAD), circumflex artery (Cx), and right coronary artery (RCA). A total of 2, 4, 8, 16, 32, and 64 points were assigned for each lesion with an obstruction level of 0–24, 25–49, 50–74, 75–89, 90–99, and 100%, respectively. If the RCA was the most obstructed artery, the lesion score for the LMCA was multiplied by a constant multiplier of 5; the lesion score for the proximal LAD and Cx was multiplied by 2.5; the score for a medial LAD lesion was multiplied by 1.5; the scores for RCA, distal LAD, and distal Cx lesions were multiplied by 1; the scores for the optus marginalis (OM1) and diagonal (D1) side branches were multiplied by 1; and the scores for other side branches were multiplied by 0.5. The total Gensini score was obtained by adding the resultant numbers. If the left system was dominant, the scores of RCA proximal, medial, and distal segment lesions were multiplied by a constant multiplier of 0.5. Ultimately, the total Gensini score was obtained numerically, which showed the severity of CAD. All coronary angiograms were evaluated by two observers who were blinded to the study. The inter- and intra-observer variability for repeated evaluations of the angiograms of 20 randomly selected patients was low (for the Gensini score: inter-observer variability, 4.8±2.9%; intra-observer variability, 4.1±2.5%).

Laboratory investigations

Venous blood samples were collected from all patients at the time of admission to the emergency department. Serum glucose; creatinine; cardiac markers, such as the MB fraction of creatine kinase (CK-MB) and troponin I; plasma hemoglobin; platelet count; and white blood cell (WBC) count were measured. Additionally, venous blood was collected after 12 hours of fasting and used to analyze the lipid profile within 24 hours. Blood samples required for ANP measurements were collected in EDTA tubes (two tubes, each containing 3 mL of blood) within 12 hours after admission from the antecubital vein while the patient was in the supine position. Plasma was obtained by the centrifugation of blood at 3,000 rpm for 10 minutes at 4±2℃ by a cooling centrifuge. Plasma samples (200 μL) were collected in small Eppendorf tubes and stored at −80℃. Plasma NT-proANP was measured using a commercially available ELISA kit [Enzyme Immunoassay for the Quantitative Determination of Human proANP (1–98) in EDTA Plasma, Heparin Plasma, Urine or Cell Culture Supernatants; Cat. No. BI-20892, Biomedica, Vienna, Austria].

Statistical analysis

Statistical analysis of the data was performed using SPSS Version 13.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables are reported as the means ± standard deviations (SDs), and categorical variables are expressed as percentages. The categorical and continuous variables were compared between the two groups using the χ^2 test and unpaired t-test, respectively. Correlation analysis was performed to assess the relationships between the LAVI, the ANP level, and other variables. For the correlation analysis, Pearson's correlation test was used to analyze data that exhibited a parametric distribution, and Spearman's correlation test was used to evaluate associations between data with a non-parametric distribution. A multivariate linear regression analysis was performed to assess the power of the relationships between the ANP level and correlating variables. A step-by-step ''backward'' method was used for the linear regression analysis. A chi-square test was used to assess associations between categorical data. The Student's t test was performed for pairwise comparisons of the ANP level. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the study population. There were no statistically significant differences in age, gender, cigarette smoking, BMI, or waist circumference between the groups. Biochemical data were not significantly different between groups, with the exception that higher levels of cardiac markers and leukocytosis were observed in patients with STEMI.

The majority of patients with STEMI enrolled in this study were middle-aged males (85.5%, mean age 56.2±10.4 years). Most of the patients (n = 62, 56.4%) had an STEMI localized at the anterior wall, and their IRA was the LAD. Additionally, most of the patients (n = 90, 81.8%) had primary PCI (mean 2.8±2.2 hours; minimum 45 minutes, maximum 6 hours), and 20 patients (18.2%) were given fibrinolytic therapy with streptokinase (1,500,000 IU over 45 minutes by intravenous infusion) within the first three hours (mean 2.4±0.8 hours) (Table 2).

Echocardiographic measurements are shown in Table 3. Conventional measurements revealed a normal LV size in both groups and impaired LV systolic function in patients with STEMI (LVEF in patients vs. controls: 49.4±7.1% vs. 60.5±5.2%, $p<0.01$). With regard to diastolic function, only

Table 1 - Demographic characteristics and laboratory values of the study population. Data are the mean ± standard deviation.

	Patients (n = 110)	Control (n = 50)	*p*-value
Age (years)	56.2±10.4	54.4±6.4	NS
Gender (male)(%)	94 (85.5%)	37 (74.0%)	NS
BMI (kg/m^2)	27.0±4.4	28.3±3.5	NS
Waist circumference (cm)	95.9±11.7	97.1±8.7	NS
Current smoker (%)	82 (74.5%)	36(72%)	NS
Hypertension (%)	31 (28.3%)	17 (34%)	NS
Diabetes mellitus (%)	19 (17.3%)	12 (24%)	NS
HR (bpm)	72.5±12.0	70.1±9.6	NS
BP (systolic/diastolic) (mmHg)	110±20/70±10	115±20/75±15	NS
Glucose (mg/dL)	154.0±53.8	146.1±45.8	NS
Creatinine (mg/dL)	0.9±0.2	1.0±0.4	NS
Hemoglobin (g/dL)	14.4±1.6	13.6±1.9	NS
Platelets (×10^3/μL)	231.6±65.2	246.3±59.2	NS
WBCs (×10^3/mL)	12.4±3.9	8.4±2.7	<0.001
LDL cholesterol (mg/dL)	120.8±39.4	119.7±27.8	NS
HDL cholesterol (mg/dL)	36.7±8.8	39.3±10.5	NS
Triglycerides (mg/dL)	140.6±44.8	136.3±41.7	NS
Peak troponin I (ng/dL)	96.1±63.5	0.3±0.2	<0.001
Peak CK-MB (ng/dL)	197.6±18.5	3.0±1.4	<0.001

BMI: body mass index; HR: heart rate; BP: blood pressure; WBC: white blood cell, LDL: low-density lipoprotein; HDL: high-density lipoprotein; CK-MB: creatine kinase isoenzyme MB.

Table 2 - Clinical and angiographic characteristics of the patients with acute STEMI.

Variable	Patients (n = 110)
MI location (anterior/other) (%)	56.4/43.6
IRA (LAD/Cx/RCA) (%)	56.4/6.4/37.2
Therapy (PCI/lytic) (%)	81.8/18.2
Pre-infarct angina (%)	70.9
Gensini score	104.0±54.6
Vessel score	1.5±0.7

STEMI: ST-segment elevation myocardial infarction; MI: myocardial infarction; IRA: infarct-related artery; LAD: left anterior descending coronary artery; Cx: left circumflex coronary artery; RCA: right coronary artery; PCI: percutaneous coronary intervention.

E/E_m increased in patients (8.7±3.3 vs. 7.9±2.8, $p=0.04$). Although LA diameters were comparable between patients and controls, the LAVI was increased in patients with STEMI (26.5±7.1 vs. 21.3±4.9 mL/m^2, $p<0.01$). The LAVI was correlated with LAAPD ($p<0.05$). Of the clinical features investigated, only the presence of hypertension was associated with LAVI (29.2 vs. 24.7 mL/m^2, $p=0.02$). There was no association between the LAVI and angiographic indexes.

NT-proANP levels were significantly higher in patients than controls (3.90±3.75 vs. 1.35±0.72 nmol/L, $p<0.001$). The Student's t test was used to assess the effect of patient demographic characteristics on plasma NT-proANP levels. NT-proANP levels were elevated in hypertensive patients and diabetic patients (5.34 vs. 3.05 nmol/L, $p=0.01$ and 5.38 vs. 3.29 nmol/L, $p=0.03$, respectively). A correlation analysis was performed to analyze the association between patients' NT-proANP levels with other variables, which showed that the NT-proANP level was correlated with age, diastolic blood pressure at the time of admission, peak troponin I value, and Gensini score (Table 4). When the NT-proANP level was examined with respect to the revascularization method used, patients who underwent PCI were found to have higher NT-proANP levels compared with those who did not undergo PCI (4.21 vs. 1.87 nmol/L for patients who underwent primary PCI vs. patients who received fibrinolytic therapy; $p=0.03$). The time until revascularization was correlated with the NT-proANP level in patients who underwent primary PCI ($p=0.02$). No associations were found between the NT-proANP level and echocardiographic parameters used to determine LV systolic and diastolic dysfunction ($p>0.05$). The LAVI was the only echocardiographic variable that correlated with the NT-proANP level (r = 0.28, $p=0.01$) (Figure 1). A linear regression analysis using stepwise backward regression was performed to show dependent and independent effects of variables that were found to correlate with the ANP level. All parameters showing a correlation (age, diastolic blood pressure at the time of admission, peak troponin I level, Gensini score, and LAVI) were included in the analysis. Age, peak troponin I level, and LAVI were independently associated with NT-proANP level (Table 5).

Table 3 - Echocardiographic measurements of the study population. Data are the mean ± standard deviation.

	Patients (n = 110)	Control (n = 50)	*p*-value
LV size and systolic function			
LVESD (cm)	3.2±0.4	3.5±0.7	NS
LVEDD (cm)	4.8±0.4	4.7±0.6	NS
IVS (cm)	0.9±0.1	1.0±0.2	NS
PW (cm)	0.9±0.1	0.9±0.1	NS
LVMI (gr/m^2)	82.2±24.2	83.9±21.4	NS
LVEF (%)	49.4±7.1	60.5±5.2	<0.001
Diastolic function			
E (cm/s)	68.2±17.1	73.7±16.8	NS
A (cm/s)	69.7±18.7	63.8±15.1	NS
DT (ms)	154.8±36.0	157.3±38.9	NS
IVRT (ms)	91.9±21.0	88.5±12.3	NS
LV MPI	0.52±0.10	0.49±0.05	NS
LV Em (cm/s)	8.3±2.1	8.9±1.6	NS
LV E/Em ratio	8.7±3.3	7.9±2.8	0.04
Atrial measurements			
LAAPD (cm)	3.6±0.4	3.8±1.2	NS
LAVI (mL/m^2)	26.5±7.1	21.3±4.9	0.001

LVESD: left ventricle end-systolic diameter; LVEDD: left ventricle end-diastolic diameter; IVS: interventricular septal thickness; PW: left ventricular posterior wall thickness; LVMI: left ventricular mass index; LVEF: left ventricular ejection fraction; LV: left ventricle; E: peak mitral valve flow velocity during the early rapid filling phase; A: peak mitral valve flow velocity during atrial contraction; DT: diastolic time; IVRT: isovolumetric relaxation time; MPI: myocardial performance index; Em: early diastolic velocity; LAAPD: left atrial antero-posterior diameter; LAVI: left atrial volume index.

Table 4 - Correlations of NT-proANP with other variables in patients with acute STEMI.

Variable	Correlation coefficient (r)	*p*-value
Age (years)	0.235	0.02
Peak troponin I level (ng/dL)	0.273	0.01
Gensini score	0.258	0.01
IVS thickness (cm)	0.239	0.01
LAVI (mL/m^2)	0.283	0.01

NT-proANP: N-terminal pro-atrial natriuretic peptide; STEMI: ST-segment elevation myocardial infarction; IVS: interventricular septal thickness; LAVI: left atrial volume index.

DISCUSSION

In this study, we evaluated LAVI and plasma NT-proANP in patients with STEMI. The level of ANP and the amount of LA dilation are strong and independent predictors of morbidity and mortality during STEMI (6,10). Although the relationship between LV characteristics and the NT-proANP level has been demonstrated previously, this is the first study to identify associations between LAVI, NT-proANP level, and clinical data, such as MI location, IRA, and the severity and extent of CAD in STEMI. The results of this study reveal that both the LAVI and NT-proANP level are affected to similar degrees during STEMI and seem compatible with each other.

The dimensions and functions of the atria, particularly the LA, have clinical significance in many cardiovascular

Table 5 - Variables associated with NT-proANP levels in patients with STEMI (Nagelkerke $R^2=0.247$ for the multivariate regression model).

Variable	β	*p*-value
Age (years)	0.289	0.01
Peak troponin I levels (ng/dL)	0.364	0.01
LAVI (ml/m^2)	0.232	0.03

NT-proANP: N-terminal peptide of proatrial natriuretic peptide, STEMI: Acute ST segment-elevation myocardial infarction, LAVI: left atrial volume index.

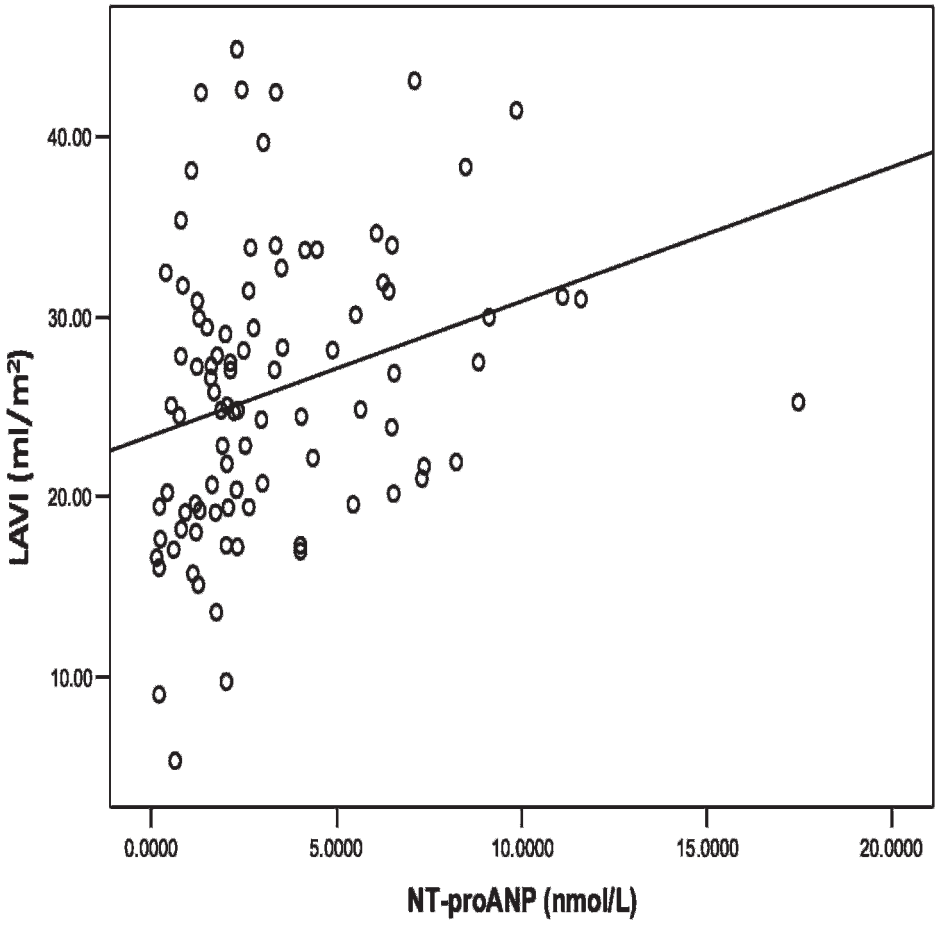

Figure 1 - Scatter plot of the patients' plasma NT-proANP levels (nmol/L) against the LAVI values (mL/m^2) (r = 0.28, $p = 0.01$).

conditions (6,18–20). The enlargement of the LA has been associated with an increased incidence of atrial fibrillation, stroke, congestive heart failure, and mortality, especially in elderly people (21). Even in young and healthy subjects (n = 2,804, mean age 59.2 years), the LA diameter is a strong and independent predictor of the development of cardiovascular events during follow-up (22). The LA size demonstrates a greater predictive value compared with LV diastolic function measurements and filling pressures, which are substantially influenced by hemodynamics (6,23). Similar to the association between the finger-stick glucose level and HbA1c value in diabetic patients, LV filling pressures, as measured by conventional and tissue Doppler imaging, are appropriate for monitoring short-term hemodynamic status, but LA measurements are more relevant for determining the average effect of the left ventricular filling pressure over time (24). Although the LA diameter is an easily quantifiable parameter by using M-mode, its accuracy in reflecting LA size is controversial due to the asymmetric structure of the LA (4,5). Currently, the LA volume measured using the modified Simpson technique from the apical four-chamber view indexed to the body surface area (LAVI) is the preferred method for LA quantification (5). A LAVI≥32 mL/m^2 determines abnormal diastolic function with 100% specificity and 67% sensitivity (25). In our study, the LA diameter and LAVI were correlated with each other ($p<0.05$). We did not observe an association between age, gender, BMI, and atrial measurements. The LAVI was increased in hypertensive patients (29.2 vs. 24.7 mL/m^2, $p = 0.01$). Impaired LV diastolic function in essential hypertension may account for the higher LAVI in these patients.

In patients with acute STEMI, there is an inverse relationship between LV and LA functions unless LA is affected from an ischemic event (26). LV function is reduced, while an increase in LA function is observed. While the contribution of LA to LV stroke volume is 20% in normal individuals, it increases to 35% in STEMI. Thus, atrial contraction greatly contributes to LV stroke volume and filling pressure in STEMI sufferers irrespective of impairment in ventricular function. A few studies have examined atrial changes in patients with acute STEMI (6,22,27,28). The presence of heart failure at admission, fibrinolytic therapy, moderate to severe mitral regurgitation, LV systolic dysfunction, and poor myocardial perfusion following revascularization were associated with an enlarged LA. We observed no association between MI location (anterior, inferior), the IRA (LAD, Cx, RCA), the method of reperfusion (primary PCI, fibrinolytics), and atrial dimensions. We believe that early successful revascularization of our patients, often with primary PCI, and the spontaneous recanalization observed in most of the non-intervened patients contributed to this finding. Again, vessel score, which reflects the extent of CAD, was not associated with atrial dimensions. The Gensini score, used

for the assessment of the severity of CAD, was correlated with left atrial diameter and volume ($p<0.01$). LV diastolic dysfunction associated with chronic myocardial ischemia may have resulted in increased LA dimensions. There was a positive correlation between the LAVI and the E/Em ratio, a sensitive marker of diastolic dysfunction ($p<0.05$).

Essentially, myocardial ischemia stimulates ANP release by increasing both LV end-diastolic pressure and wall tension (29). The correlation observed between the maximum CK-MB level (an index of infarction size) and ANP level during the early phase of STEMI (the first 6 hours) led us to hypothesize that ANP release is essentially an indicator of the severity of the infarction and that ANP is released from ischemic cardiac tissues (30). However, no association was found between ANP level and infarct location, the number of vessels involved, or whether reperfusion could be achieved. The plasma ANP level measured on the first day of MI was correlated with the mean right atrial pressure, pulmonary artery pressure, and PCWP recorded during right cardiac catheterization, but they did not change in patients without a decreased cardiac index (31). Elevated ANP levels during STEMI is associated with the development of heart failure and increased cardiac mortality (10,31,32). In our study, NT-proANP levels were nearly 2.5 times higher in patients than controls. ANP was also elevated in elderly, hypertensive, and diabetic patients. Our findings do not differ from those of previous studies that demonstrated elevated natriuretic peptide in subjects with essential hypertension, especially when left ventricular hypertrophy and DM are present (33,34). We found that NT-proANP was more likely to correlate with the peak level of troponin I, a more sensitive marker, than with CK-MB. We did not observe any association between the location of MI (e.g., anterior or inferior), IRA or the number of vessels involved (as quantified by the vessel score), and NT-proANP level. The observed correlation between the Gensini score, which is an indicator of CAD severity, and the NT-proANP level may have resulted from lower EF values in patients with higher Gensini scores. NT-proANP was also higher in patients who underwent primary PCI compared with patients administered fibrinolytic therapy ($p=0.03$). PTCA-induced myocardial ischemia may have been the cause of this elevation. In patients undergoing primary PCI, the time elapsed from the onset of pain to revascularization was correlated with ANP level ($p=0.02$). It is possible that the size of myocardial damage and the NT-proANP level increased due to delays in performing the procedure.

When the previous studies that examined the associations between ANP level and echocardiographic parameters in patients with STEMI were revised, the NT-proANP level obtained during hospitalization was found to correlate with LVESD and EF in patients receiving thrombolytic therapy (10). In a more recent study, Elmas et al. evaluated the plasma levels of midregional pro–A-type natriuretic peptide (MR-proANP), a newly developed assay for ANP quantification, and NT-proBNP in 102 patients with a history of STEMI (35). They demonstrated that MR-proANP was the strongest predictor of LVEF, even superior to NT-proBNP. However, Nagaya et al. measured post-infarction natriuretic peptide without taking into account the success of revascularization or the therapy administered, and they failed to show a relationship between plasma ANP level and changes in LV size and function (36). Similarly, we did not find an association between NT-proANP level and LV diameter or EF in our study. This finding could be explained by the preserved LV function in most patients (mean LVEF = 49.4 ± 7.1%) due to timely and successful reperfusion. LAVI was the only echocardiographic variable that correlated with NT-proANP level ($r=0.283$, $p=0.01$). Furthermore, it was independently associated with NT-proANP level. The results of our study are consistent with the results of the ROMICAT Trial, which reported an independent association between MR-proANP concentration and LA enlargement but not between MR-proANP and LV measures in adult patients without heart failure (37).

Based on this association between NT-proANP and LAVI, we may suggest that the major source of ANP after an acute STEMI is the left atrium. The clinical importance of this result is that measuring LAVI as part of the routine echocardiographic examination in patients who have suffered an acute STEMI could provide valuable clinical and prognostic data. Although the long-term prognostic significance of increased LAVI in STEMI is well known, elevated NT-proANP, which is also a marker of adverse cardiovascular outcomes, may help explain the unfavorable results associated with LA dilation.

Study limitations

This study had several limitations, the most significant of which was the relatively small sample size. LA size could have been estimated with newer techniques, such as real-time three-dimensional echocardiography, but we chose to use 2D echocardiography due to limited experience with the former technique in these patients. The other limitation was the absence of LV pressure data. The LA, LV filling, and end-diastolic pressures could have been measured invasively, but we evaluated the Doppler parameters of diastolic function instead. These measures accurately predict LV pressures (6). Additionally, the contribution of medical therapy to the changes in LA size and NT-proANP level was not considered. Another potential limitation of the study is that we did not assess BNP. Lim et al. reported the value of BNP together with echocardiographic measurements in acute STEMI patients; therefore, we did not measure serum BNP (38). The current study was not designed to investigate mortality or major adverse cardiac events but instead focused on the possible association between NT-proANP level and LA size in patients with STEMI.

Increased left atrial volume and ANP, a major peptide released from atria, are strong predictors of post-MI survival. Whereas ANP measurement is expensive and cumbersome in clinical practice, the LAVI may be easily quantified during routine echocardiographic examination. In this study, we demonstrated that plasma NT-proANP increased due to enlargement of the LA in STEMI patients. The results of this study reveal a strong association between LAVI and NT-proANP. It may be beneficial to assess the LAVI, which is simple and convenient, instead of NT-proANP in patients with acute STEMI.

AUTHOR CONTRIBUTIONS

Bacaksiz A participated in the study design, carried out the echocardiographic examinations, contributed to the writing of the manuscript, and drafted the manuscript. Vatankulu MA participated in the study design, carried out the echocardiographic examinations, and contributed to the writing of the manuscript. Kayrak M conceived the study and performed the statistical analysis. Telli HH contributed to the study design, reviewed

the manuscript, and contributed to the oversight and organization. Ayhan SS participated in the study design and in the revision of the manuscript. Sonmez O participated in the study design and contributed to the writing of the manuscript. Alp A and Buyukbas S participated in the study design and performed the biochemical measurements. All authors approved the final version of the manuscript.

REFERENCES

1. Welch TD, Yang EH, Reeder GS, Gersh BJ. Modern management of acute myocardial infarction. Curr Probl Cardiol. 2012;37(7):237-310, http://dx.doi.org/10.1016/j.cpcardiol.2012.03.002.
2. Souza LP, Campos O, Peres CA, Machado CV, Carvalho AC. Echocardiographic predictors of early in-hospital heart failure during first ST-elevation acute myocardial infarction: does myocardial performance index and left atrial volume improve diagnosis over conventional parameters of left ventricular function? Cardiovasc Ultrasound. 2011;9:17, http://dx.doi.org/10.1186/1476-7120-9-17.
3. Choong CY, Hermann HC, Weymann AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. J Am Coll Cardiol. 1987;10(4):800-8, http://dx.doi.org/10.1016/S0735-1097(87)80273-5.
4. Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. Ochsner J. 2009;9(4):191-6.
5. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63, http://dx.doi.org/10.1016/j.echo.2005.10.005.
6. Møller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: a powerful predictor of survival after myocardial infarction. Circulation. 2003;107(17):2207-12, http://dx.doi.org/10.1161/01.CIR.0000066318.21784.43.
7. Hoffmann U, Brueckmann M, Bertsch T, Wiessner M, Liebetrau C, Lang S, et al. Increased plasma levels of NT-proANP and NT-proBNP as markers of cardiac dysfunction in septic patients. Clin Lab. 2005;51(7-8):373-9.
8. Clerico A, Giannoni A, Vittorini S, Passino C. Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. Am J Physiol Heart Circ Physiol. 2011;301(1):H12-20, http://dx.doi.org/10.1152/ajpheart.00226.2011.
9. Bartkowiak R, Wozakowska-Kapłon B, Janiszewska G. Plasma NT-proANP in patients with persistent atrial fibrillation who underwent successful cardioversion. Kardiol Pol. 2010;68(1):48-54.
10. Magga J, Puhakka M, Hietakorpi S, Punnonen K, Uusimaa P, Risteli J, et al. Atrial natriuretic peptide, B-type natriuretic peptide, and serum collagen markers after acute myocardial infarction. J Appl Physiol. 2004;96(4):1306-11, http://dx.doi.org/10.1152/japplphysiol.00557.2003.
11. Katayama T, Nakashima H, Furudono S, Honda Y, Suzuki S, Yano K. Evaluation of neurohumoral activation (adrenomedullin, BNP, catecholamines, etc.) in patients with acute myocardial infarction. Intern Med. 2004;43(11):1015-22, http://dx.doi.org/10.2169/internalmedicine.43.1015.
12. Nakamura M, Arakawa N, Yoshida H, Funakoshi T, Chiba M, Makita S, et al. Prognostic Implications of Plasma Levels of Atrial Natriuretic Factor in Patients with Acute Myocardial Infarction. Intern Med. 1993;32(2):112-5, http://dx.doi.org/10.2169/internalmedicine.32.112.
13. Svanegaard J, Johansen JB, Klitgaard NA, Thayssen P, Haghfelt T. Correlation between serial changes in left-sided heart chambers and atrial natriuretic peptide and N-terminal pro atrial natriuretic peptide after a first myocardial infarction. An echocardiographic study. Scand Cardiovasc J. 1999;33(6):355-61.
14. Taylor J. Third universal definition of myocardial infarction. Eur Heart J. 2012;33(20):2506-7.
15. Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, et al. Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation. 1979;60(3):547-55, http://dx.doi.org/10.1161/01.CIR.60.3.547.
16. Sullivan DR, Marwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. Am Heart J. 1990;119(6):1262-7, http://dx.doi.org/10.1016/S0002-8703(05)80173-5.
17. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983;51(3):606, http://dx.doi.org/10.1016/S0002-9149(83)80105-2.
18. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2002;40(8):1425-30, http://dx.doi.org/10.1016/S0735-1097(02)02305-7.
19. Rossi A, Tomaino M, Golia G, Sentini F, Pentiricci S, Marino P, et al. Usefulness of left atrial size in predicting postoperative symptomatic improvement in patients with aortic stenosis. Am J Cardiol. 2000;86(5):567-70, http://dx.doi.org/10.1016/S0002-9149(00)01019-5.
20. Jikuhara T, Sumimoto T, Tarumi N, Yuasa F, Hattori T, Sugiura T, et al. Left atrial function as a reliable predictor of exercise capacity in patients with recent myocardial infarction. Chest. 1997;111(4):922-8, http://dx.doi.org/10.1378/chest.111.4.922.
21. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, Gersh BJ, et al. Usefulness of left atrial volume in predicting first congestive heart failure in patients > or = 65 years of age with well-preserved left ventricular systolic function. Am J Cardiol. 2005;96(6):832-6, http://dx.doi.org/10.1016/j.amjcard.2005.05.031.
22. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: The Strong Heart Study (SHS). Am Heart J. 2006;151(2):412-8, http://dx.doi.org/10.1016/j.ahj.2005.04.031.
23. Beinart R, Boyko V, Schwammenthal E, Kuperstein R, Sagie A, Hod H, et al. Long-term prognostic significance of left atrial volume in acute myocardial infarction. J Am Coll Cardiol. 2004;44(2):327-34, http://dx.doi.org/10.1016/j.jacc.2004.03.062.
24. Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. J Am Coll Cardiol. 2003;42(7):1206-7, http://dx.doi.org/10.1016/S0735-1097(03)00956-2.
25. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left Atrial Volume as a Morphophysiologic Expression of Left Ventricular Diastolic Dysfunction and Relation to Cardiovascular Risk Burden. Am J Cardiol. 2002;90(12):1284-9, http://dx.doi.org/10.1016/S0002-9149(02)02864-3.
26. Sigwart U, Grbic M, Goy J, Kappenberger L. Left atrial function in acute transient left ventricular ischemia produced during percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. Am J Cardiol. 1990;65(5):282-6, http://dx.doi.org/10.1016/0002-9149(90)90288-C.
27. Ahn SG, Shin JH, Koh BR, Choi JH, Kang SJ, Choi BJ, et al. Impact of myocardial perfusion on left atrial remodeling following primary angioplasty for acute myocardial infarction. Coron Artery Dis. 2006;17(7):597-603, http://dx.doi.org/10.1097/01.mca.0000236281.74361.d4.
28. Feinberg MS, Boyko V, Leor J, Kuperstein R, Sagie A, Hod H, et al. Differential value of left atrial systolic and diastolic volumes as independent predictors of congestive heart failure or early death in acute myocardial infarction. Heart. 2006;92(3):397-8.
29. Bergeron S, Møller JE, Bailey KR, Chen HH, Burnett JC, Pellikka PA. Exertional Changes in Circulating Cardiac Natriuretic Peptides in Patients with Suggested Coronary Artery Disease. J Am Soc Echocardiogr. 2006;19(6):772-6, http://dx.doi.org/10.1016/j.echo.2006.01.010.
30. Tan AC, van Loenhout TT, Lamfers EJ, Hooghoudt TE, Kloppenborg PW, Benraad TJ. Atrial natriuretic peptide after myocardial infarction. Am Heart J. 1989;118(3):490-4, http://dx.doi.org/10.1016/0002-8703(89)90262-7.
31. Hara H, Ogihara T, Nakamaru M, Rakugi H,Tateyama H. Changes in the levels of plasma atrial natriuretic peptide, hemodynamic measurements, and the levels of vasoactive hormones during the clinical course of congestive heart failure. Clin Cardiol. 1988;11(11):743-7, http://dx.doi.org/10.1002/clc.4960111104.
32. Hall C, Rouleau JL, Moyè L, de Champlain J, Bichet D, Klein M, Sussex B, et al. N-Terminal Proatrial Natriuretic Factor. An Independent Predictor of Long-term Prognosis After Myocardial Infarction. Circulation. 1994;89(5):1934-42.
33. Nannipieri M, Seghieri G, Catalano C, Prontera T, Baldi S, Ferrannini E. Defective regulation and action of atrial natriuretic peptide in type 2 diabetes. Horm Metab Res. 2002;34(5):265-70, http://dx.doi.org/10.1055/s-2002-32141.
34. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. Hypertension. 1996;28(1):22-30, http://dx.doi.org/10.1161/01.HYP.28.1.22.
35. Elmas E, Brueckmann M, Lang S, Kälsch T, Haghi D, Sueselbeck T, et al. Midregional pro-atrial natriuretic peptide is a useful indicator for the detection of impaired left ventricular function in patients with coronary artery disease. Int J Cardiol. 2008;128(2):244-9.
36. Nagaya N, Nishikimi T, Goto Y, Miyao Y, Kobayashi Y, Morii I, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am Heart J. 1998;135(1):21-8, http://dx.doi.org/10.1016/S0002-8703(98)70338-2.
37. Truong QA, Siegel E, Karakas M, Januzzi JL Jr, Bamberg F, Mahabadi AA, et al. Relation of natriuretic peptides and midregional proadrenomedullin to cardiac chamber volumes by computed tomography in patients without heart failure: from the ROMICAT Trial. Clin Chem. 2010;56(4):651-60, http://dx.doi.org/10.1373/clinchem.2009.138586.
38. Lim TK, Hayat SA, Gaze D, Celik E, Collinson P, Senior R. Independent value of echocardiography and N-terminal pro-natriuretic Peptide for the prediction of major outcomes in patients with suspected heart failure. Am J Cardiol. 2007;100(5):870-5, http://dx.doi.org/10.1016/j.amjcard.2007.04.027.