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Prediction of postoperative atrial fibrillation with left atrial mechanical functions and NT-pro ANP levels after coronary artery bypass surgery: A three-dimensional echocardiography study

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Objective: Postoperative AF (POAF) is the most common cause of morbidity after coronary artery bypass surgery. In this study, we aimed to show the relationship between POAF and N-terminal pro-atrial natriuretic peptide (NT-pro ANP) levels and the relationship between mechanical functions and left atrial volume measured using preoperative three-dimensional echocardiography (3D ECHO) among patients that will undergo isolated coronary artery bypass grafting (CABG) in elective conditions.

Method: Sixty-six consecutive patients (51 male, 15 female) who were decided to undergo CABG and had normal sinus rhythm were involved in the study. Patients were followed by continuous electrocardiography monitoring and daily electrocardiogram. LA volume and mechanical functions were calculated with 3D ECHO. In addition, for the analysis of plasma levels of NT-pro ANP, blood samples were collected before the surgery.

Results: During follow-up after the operation, 15 patients (22.7%) had postoperative atrial fibrillation. LA Vmax, Vmin, VpreA values were higher ($P < .001$, $P = .004$, $P < .001$ respectively) Also in POAF-developed group and SR group, LAVI values were 27.56 ± 4.2 and 20.7 ± 4.64 mL/m^2, respectively ($P < .001$). In POAF-developing group, NT-pro ANP levels were significantly higher ($P < .001$). In multiple logistic regression analysis, age ($\beta = 0.355$, $P = .007$) and LAVI ($\beta = 0.668$, $P = .012$) are independent predictors of POAF.

Conclusion: It was found that 3D echocardiography can be used as a helping noninvasive method to show subclinical atrial volume and mechanical dysfunction in patients undergoing CABG. Also, blood levels of NT-pro ANP in POAF group were increased.

KEYWORDS
atrial fibrillation, coronary artery bypass surgery, left atrial volume, three-dimensional echocardiography

1 | INTRODUCTION

The most common complication in patients undergoing open heart surgery is postoperative arrhythmias. Atrial fibrillation (AF) after coronary artery bypass grafting (CABG) occurs in 20%–40% of patients.[1] Postoperative AF (POAF) is the most common cause of postoperative morbidity after coronary surgery because of decreased cardiac output associated with AF, hypotension and congestive heart failure, and thromboembolic events.[2]

LA volume and mechanical functions reflect the severity of LV diastolic dysfunction.[3] During ventricular diastole, LA is exposed directly to the LV pressure through the opened mitral valve. In decreasing LV compliance, LA pressure and atrial contribution are increased for continued stroke volume.[4] It is known that LA size and functions are influenced by conditions such as cardiomyopathy, hypertension, valve diseases and arrhythmia, especially the LV systolic and diastolic functions, and it is also an important indicator of mortality and morbidity.

Atrial natriuretic peptide (ANP) is a peptide hormone with strong natriuretic, diuretic, and vasoactive properties that are synthesized in muscle cells of the cardiac atrium and released into the plasma.[5] The ANP system is activated in cardiac decompensations where there is increased LV end-diastolic pressure and atrial diameter.[6] The increase in ANP concentration is proportional to the degree of atrial distention.

Parallel to the increase in echocardiographic image quality, three-dimensional echocardiography (3D ECHO) has been introduced in recent years. Although there are many studies on 2D ECHO that assess the relationship between newly developed AF after isolated CABG and preoperative LA volume and mechanical functions, there are no studies available in the literature regarding 3D ECHO, which is superior to 2D ECHO in volumetric evaluation.

Therefore, this study is aimed to demonstrate the relationship of LA volume and mechanical functions assessed using preoperative 3D ECHO and the measured N-terminal pro-atrial natriuretic peptide (NT-pro ANP) level with POAF in patients undergoing isolated CABG under elective conditions.

2 | METHOD

The study included 66 patients who applied to the cardiology polyclinic with a typical chest pain between October 2013 and March 2014, whom were planned to undergo elective coronary angiography based on the examinations performed, whom were decided to undergo CABG as concluded by the council held together with the Cardiology and Cardiovascular Surgery department and who signed a written consent form. The study was approved by the local Ethics Committee. The study was planned in accordance with the Helsinki declaration. All of the patients were prospectively monitored until discharge following CABG, and the patients with isolated CABG who were included in the study were divided into two groups—patients with postoperative AF (POAF Group; n = 15 patients) and patients without postoperative AF (SR Group; n = 51 patients). All patients' data were regularly recorded.

The study excluded patients with atrial fibrillation as detected by 12-lead electrocardiogram taken preoperatively, patients who had undergone transcatheter ablation for AF, patients with moderate or severe heart valve disease, patients who had myocardial infarction within the last 1 month, patients with congestive heart failure with ejection fraction (EF) <40%, patients who had undergone emergency operation, patients with a history of renal and hepatic insufficiency, patients with a history of atrial dysrhythmia, patients with congenital heart diseases, patients with poor echocardiographic image quality, and patients who refused to participate in the study.

2.1 | Definition

The presence of DM, previous diagnosis of DM or DM according to "American Diabetes Association" criteria, is defined as fasting blood glucose level of 126 mg/dL or more, and/or oral antidiabetic and/or insulin use.[7] In accordance with the "Adult Treatment Panel III" (ATP III) guidelines, total cholesterol >200 mg/dL or LDL cholesterol >100 mg/dL or the use of lipid-lowering drugs were considered as hyperlipidemia.[8] In accordance with the "Joint National Committee VII" (JNC VII) guidelines, HT is defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or use of blood pressure-lowering drugs.[9] Patients' height and body weight were measured, and body mass index and body surface areas were calculated. Body mass index is calculated by dividing a person's weight by the square of his or her height (kg/m^2). Continuous ECG monitoring was performed postoperatively in the intensive care unit for each case. After the patients were discharged from the intensive care unit, residents or nurses performed rhythm control by manually palpating their radial pulses at least four times a day. In addition to this routine evaluation performed four times a day, additional physical examinations were performed in clinically suspected patients. Routine ECG checks were performed after each operation and on postoperative day 1, 2, and 4. Additional ECG images were taken when patients developed symptoms such as tachycardia or irregular rhythm. AF was diagnosed when 12-lead ECG showed irregular QRS complexes, as well as fibrillatory "P"-waves varying in size, shape, and timing. Postoperative AF was defined as AF emerged at any time after the operation and confirmed by physician assessment and 12-lead ECG.

2.2 | Echocardiography

Transthoracic echocardiographic evaluations of all patients included in the study were performed using echocardiography device Philips Medical Systems iE33 (Bothell, WA, USA). 2D ECHO analyses were performed using a 2.5 MHz S5-1 transducer. In the left lateral decubitus position, parasternal long and short axis, apical four- and two-chamber images were obtained. Transthoracic echocardiographic measurements were made in accordance with the AHA and ESC Heart Cavity Measurement Guideline. Ejection fraction was calculated according to modified Simpson's method. The apical four-chamber view was acquired by PW Doppler method with the sample volume positioned at the tip of the mitral valve leaflets which allowed to calculate the maximum velocities of early diastolic peak transmitral flow velocity (E) and late diastolic peak transmitral flow velocity (A) in cm/s. The E/A ratio was calculated. E-wave deceleration time (DT) is calculated in milliseconds (ms). Again, mitral lateral annulus peak early diastolic (Em), peak late diastolic (Am), and systolic (S)-wave velocities were measured in cm/s by tissue Doppler in apical four-chamber sections. Subsequently, the same tissue was measured as myocardial isovolumetric relaxation time (IVRT) and ejection time (ET) (ms) in the Doppler image. E/Em and Em/Am ratios were also calculated.

TABLE 1 Preoperative characteristics in patients undergoing CABG

	AF	non-AF	*P* -value
Age (years)	71.6 ± 6.23	58.2 ± 8.3	**<.001**
Sex female, n, (%)	4 (26.7%)	11 (21%)	.731
Smoking n (%)	7 (46.7%)	28 (54.9%)	.581
Body mass index (kg/m^2)	25.8 ± 3.24	26.5 ± 2.63	.645
Body surface area (m^2)	1.83 ± 0.07	1.86 ± 0.09	.193
Hypertension %	7 (46.7%)	25 (49%)	.873
Hyperlipidemian %	12 (80%)	32 (62.7%)	.213
History of PCI n%	3 (20%)	11 (21.6%)	.898
Diabetes mellitus n%	5 (33.3)	22 (43.1%)	.497
Glucose (mg/dL)	131.1 ± 62.1	132.1 ± 62.5	.976
Creatinine (mg/dL)	0.87 ± 0.13	0.91 ± 0.16	.419
Total cholesterol (mg/dL)	192.8 ± 32.5	174.6 ± 41.9	.126
LDL cholesterol (mg/dL)	121.7 ± 31.45	106.7 ± 33.6	.129
HDL cholesterol (mg/dL)	37.9 ± 9.85	34.7 ± 7.93	.195
Triglycerides (mg/dL)	173.9 ± 94.9	165.1 ± 75.9	.842
COPD n%	5 (33.3)	7 (13.7)	.125

Bold value indicates statistical significance.
PCI = percutaneous coronary intervention; LDL = low-density lipoprotein; HDL = high-density lipoprotein; COPD = chronic obstructive pulmonary disease.

2.3 | Real time 3D echocardiographic evaluation

After ECG monitorization, full volume live three-dimensional images were obtained over 4–5 consecutive cardiac beats using X3 matrix-array transducer (1–3 MHz) with the patient breath holding at the end of expiration and saved as a DICOM format in DVD for later use. The obtained images were uploaded to the device at a different time and run through Advanced Qualification Program (QLab-Philips version 7.1) available on the device. Vmax, the largest volume at end-systole immediately before mitral valve opening, was measured at the end of the T-wave on the ECG and just before mitral valve opening. Vmin, the smallest LA volume at end-diastole just before the mitral valve closure, was measured at the beginning of the QRS-wave and at the mitral valve closure. VpreA, the volume before the mitral valve reopening, was measured at the beginning of the P-wave in the ECG. After these measurements were made, LA functions were calculated by the specified formulas (3). Accordingly, left atrial volume parameter values (LA Total Stroke Volume (TSV): V max-V min, LA Total Emptying Fraction (TEF): TSV/V max × 100, LA Active Stroke Volume (ASV) V pre-A-V min, SA Active Emptying Fraction (AEF): ASV/VpreA × 100, LA Passive Emptying Fraction (PEF) (V max-V preA)/V max × 100, LA Expansion Index (EI) TSV/Vmin × 100, LA Maximum Volume Index (LAVI) Vmax/Body Surface Area) were obtained using the following formulas.

2.4 | Measurement of N-terminal pro-atrial natriuretic peptide levels

Plasma NT-pro ANP level was measured by a commercially available ELISA kit (Enzyme Immunoassay For In Vitro Quantitative Measurement of NT-pro ANP (SEA484Hu 96 Tests) in human serum, plasma, tissue homogenates, cell lysates, cell culture supernates, and other biological fluids. Cloud-Clone Corp Houston, TX, USA).

2.5 | Statistical analysis

The results obtained in the study were statistically evaluated using SPSS 17.0 (SPSS, Inc, Chicago, IL, USA) for windows. The mean ± standard deviation was used to define the numerical (quantitative) variables, and the number (n) and percentage (%) were used to define the categorical variables. In the comparison of SR and POAF groups, the Shapiro-Wilk Test of Normality was used to determine if the variables were normally distributed. Unpaired *t* test was used for comparison of quantitative variables with normal distribution in the statistical evaluation and Mann-Whitney U test was used for comparison of quantitative variables without normal distribution. The relationship between quantitative variables was tested by Pearson and Spearman's correlation analysis. Pearson chi-square test and Fisher's exact chi-square test were used to compare qualitative variables. The performance of NT-pro ANP in differentiating between patients and healthy individuals was demonstrated by ROC analysis. At the same time, the predictors of the POAF were assessed by performing a multivariate logistic regression analysis. Statistical significance level was accepted at $P < .05$.

3 | RESULTS

The study included a total of 66 (51 male, 15 female) patients who were decided to undergo isolated elective CABG based on the result of coronary angiography. During follow-up, 15 patients (22.7%) developed atrial fibrillation after the operation. Comparisons of the demographic characteristics and 2D echocardiography parameters of all the individuals included in the study are shown in Tables 1 and 2. When the main characteristic features of the cases were examined, the mean age of the POAF group was found to be statistically significantly higher than that of sinus rhythm group (58.2 ± 8.3 years vs 71.6 ± 6.23 years, $P < .001$).

The comparison of the two groups in terms of 3D ECHO LA volume and mechanical function parameters is shown in Table 3. When LA functions were analyzed by 3D ECHO, LA Vmax, Vmin, VpreA, and ASV values were found to be higher in the POAF group with the difference between two groups being statistically significant ($P < .001$ and $P = .004$, $P < .001$ and $P < .001$, respectively). In the POAF-developing group and the SR group, the LAVİ values were 27.56 ± 4.2 and 20.7 ± 4.64 mL/m^2, respectively. The difference between the groups was statistically significant ($P < .001$). EI, TEF, and PEF percentages were statistically significantly lower in the

TABLE 2 Preoperative 2D echocardiography data

	AF	non-AF	*P*-value
E rate (cm/sn)	69.8 ± 16.7	61.42 ± 20.0	.062
A rate (cm/sn)	80.3 ± 17.82	70.78 ± 16.5	.078
E/A ratio	0.91 ± 0.31	0.93 ± 0.49	.581
Em	8.73 ± 2.31	8.52 ± 3.46	.525
Am	10.67 ± 3.68	10.6 ± 3.04	.860
E/Em ratio	8.44 ± 2.59	7.99 ± 3.83	.188
LV EF (%)	58.07 ± 3.15	58.33 ± 4.89	.340
LVEDD (cm)	47.93 ± 2.37	47.33 ± 3.94	.232
LVESD (cm)	29.93 ± 3.08	29.27 ± 4.6	.193
IVS (cm)	1.02 ± 0.06	1.06 ± 0.12	.316
PWD (cm)	0.92 ± 0.06	0.96 ± 0.09	.208
sPAP (mm Hg)	29.33 ± 3.33	27.69 ± 3.18	.086
LAD (cm)	37.13 ± 2.56	35.86 ± 3.29	.174

E rate = early diastolic filling; A rate = late diastolic filling; LV EF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; IVS = interventricular septum; PWD = posterior wall diameter; sPAB = systolic pulmonary artery pressure; LAD = left atrial diameter.

TABLE 3 Comparison of preoperative 3D echocardiographic parameters and NT-pro ANP levels

Parameter	POAF	non-AF	*P*-value
Vmax (mL)	50.37 ± 7.5	39.45 ± 9.4	**<.001**
Vmin (mL)	22.61 ± 4.22	17.39 ± 6.25	**.004**
VpreA (mL)	32.72 ± 5.25	24.91 ± 7.99	**<.001**
ASV (mL)	10.11 ± 1.72	7.52 ± 2.20	**<.001**
TSV (mL)	26.37 ± 4.78	24.41 ± 7.05	.472
AEF (%)	31.08 ± 4.19	30.68 ± 4.11	.815
TEF (%)	53.16 ± 4.69	58.76 ± 4.19	**<.001**
PEF (%)	34.04 ± 4.35	40.55 ± 4.0	**<.001**
EI (%)	117.81 ± 15.36	144.54 ± 22.67	**<.001**
LAVI (mL/m^2)	27.56 ± 4.2	20.70 ± 4.64	**<.001**
NT-pro ANP (pg/mL)	592.24 ± 167.03	365.17 ± 149.83	**<.001**

Bold values indicate statistical significance.
Data are defined as mean ± standard deviation.
Vmax = LA maximal volume; Vmin = LA minimum volume; VpreA = LA atrial precontraction volume; ASV = LA active stroke volume; TSV = LA total stroke volume; AEF = LA active emptying fraction; TEF = LA total emptying fraction; PEF = LA passive ejection fraction; EI = LA expansion index; LAVI = LA volume index.

POAF group compared to the SR group ($P < .001$). NT-pro ANP values were different (592.24 ± 167.03 pg/mL, 365.17 ± 149.83 pg/mL $P < .001$).

POAF showed positive correlation with Vmax, Vmin, Vprea, ASV, and LAVI ($P < .001$, for all) and negative correlation with PEF ($P = .003$), TEF ($P = .002$) and EI ($P = .001$). When multivariate logistic regression analysis was performed, age (β = 0.355, 95% CI 1.104–1.842, $P = .007$) and LAVI (β = 0.668, 95% CI 1.160–3.277, $P = .012$) were found to be independent predictors for the development of post-CABG AF (Table 4).

TABLE 4 Univariate and multivariate analysis parameters for POAF predictors

	r	*P*	β (95% CI)	*P*
Age	.590	**<.001**	0.355 (1.10–1.84)	**.007**
Vmax	.441	**<.001**		
Vmin	.409	**.001**		
Vprea	.422	**<.001**		
TSV	.089	.472		
TEF	−.508	**<.001**		
ASV	.476	**<.001**		
AEF	.029	.815		
EI	−.498	**<.001**		
PEF	−.547	**<.001**		
NT-pro ANP	.503	**<.001**		
LAVI	.544	**<.001**	0.668 (1.16–3.28)	**.012**

Bold values indicate statistical significance.
Vmax = LA maximal volume; Vmin = LA minimum volume; VpreA = LA atrial precontraction volume; TSV = LA total stroke volume; TEF = LA total emptying fraction; ASV = LA active stroke volume; AEF = LA active emptying fraction; EI = LA expansion index; PEF = LA passive ejection fraction; NT-pro ANP = N-terminal pro-atrial natriuretic peptide; LAVI = LA volume index.

4 | DISCUSSION

In our study, the incidence of AF after CABG was found to be 22.7% and age was determined to be an effective risk factor for the development of AF. However, left atrial mechanical functions were impaired in the POAF after CABG group. In addition, there appeared to be a strong positive correlation between POAF development and NT-pro ANP with respect to Vmax, Vmin, and TEF correlations. Age and LAVI have been shown to be independent predictors of POAF development.

AF is the most common arrhythmia that is seen after CABG. Although POAF is often self-limiting and has a good course in most cases, it is associated with significant complications such as systemic embolism and hemodynamic deterioration, leading to an increase cost and length of stay in the hospital.[10] Structural changes such as atrial dilatation, loss of nodal fibers, muscle atrophy, increase in fibrous tissue, and fat tissue in the sinoatrial node, local interstitial amyloid deposits in the atria occur associated with aging, which are known to increase the susceptibility to atrial fibrillation. Zangrillo et al. have shown that older age is a risk factor for the development of postoperative AF after coronary surgery.[11] Similarly, in our study, advanced age has been associated with a higher incidence of POAF and is shown to be an independent predictor for the development

of POAF. LA volume has been shown to be a prognostic factor in determining adverse cardiovascular events in many diseases.[12] A Framingham Heart Study showed that even a 5 mm increase in LA was associated with a 39% increase in the risk of atrial fibrillation.[13] Recently, real time three-dimensional echocardiography has emerged as a new imaging technique for various cardiac diseases and has been shown to be superior to 2D measurements.[14,15] In diastolic dysfunction, increased Vmax is associated with elevated LV filling pressure whereas increased Vmin was reported to be due to atrial contraction failure.[16] The study by Russo et al. has shown that LA Vmax and Vmin values increase as the diastolic dysfunction increases. Recently, it has been shown that Vmin and its increased values are more significant than Vmax for the development of atrial fibrillation after cardiac surgery.[17] Similarly, in our study, Vmax and Vmin were found to be higher in the POAF group and strongly correlated with NT proANP.

The active function of the left atrium is determined primarily by the contractility of its own myocardium and partly by the VpreA according to the Frank-Starling law.[18] Impaired LA passive emptying function also results in a large residual LA volume prior to active contraction. Therefore, ASV and VpreA values are likely to be higher secondary to the impaired LA function in the passive emptying phase. In our study, passive LA systolic functions (PEF), (EI) and (TEF) results were observed at lower levels in the POAF group compared to the SR group. It was observed that the ASV and VpreA values secondary to this impaired function were higher than the SR group in support of this finding. Framingham Heart Study revealed that SA enlargement was a strong predictor for the development of AF.[13] Osranek et al. have shown that SA volume measurement, a more reliable index of left atrial enlargement in a patient population undergone cardiac surgery, is a strong marker for the development of AF.[19] In our study, LAVI was found to be a strong predictor of POAF development in multiple regression analysis.

NT-pro ANP has been shown to be an independent marker of atrial wall tension and to have a high predictive power to predict adverse events.[20] Hornestam et al. have indicated that NT-pro ANP levels are a biochemical marker for increased intra-atrial pressure.[21] Wang et al. emphasize that pro-ANP is a marker for AF in community-based populations. It has also been shown to be closely associated with cardiovascular morbidity and mortality.[20] In our study, NT-pro ANP level was significantly higher in patients who developed POAF than in the SR group, but it was not an independent predictor for the development of POAF, as demonstrated by multivariate analysis. We think that this may be due to insufficient number of patients.

5 | CONCLUSION

One of the most important conclusions of our study is that the parameters of LA volumes (Vmax, Vmin, VpreA) and LA active contraction functions are increased, whereas the parameters of LA passive phase functions (PEF, EI, and TEF) are decreased in the POAF group. We also believe that larger studies with NT-proANP which is correlated with POAF may provide more supportive findings.

5.1 | Study limitations

The most important limitations of our study are relatively small number of patients, single center nature of the study, and short follow-up period. To support the data from this study, large studies are needed with higher number of patients and longer-term follow-ups. Short-term AF exacerbations may have been overlooked due to post-ICU ECG follow-ups being performed according to physical examination or patient's complaint and the failure to use telemetry or ambulatory Holter electrocardiography (ECG). Besides, 3D ECHO can lead to errors in the volume measurement due to its poor definition of the endocardial border, smaller image size and angle- and operator-dependent measurement technique.

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