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The impact of percutaneous left atrial appendage closure on left ventricular diastolic function and natriuretic peptide levels

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Abstract. – OBJECTIVE: Although the efficacy and safety of left atrial (LA) appendage (LAA) closure in patients with atrial fibrillation (AF) have been well documented in randomized controlled trials and real-world experience, there are limited data in the literature about the impact of LAA closure on diastolic functions. The study aimed to examine the impact of LAA closure on diastolic function and natriuretic peptide levels in patients with AF.

PATIENTS AND METHODS: Twelve non-valvular AF patients with high risk for developing cardioembolic stroke and contraindications to warfarin underwent LAA occlusion with the WATCHMAN device (Atritech Inc., Plymouth, MN, USA). B-type natriuretic peptide levels and detailed diastolic parameters (mitral inflow velocities, deceleration time (DT), flow propagation velocity (Vp), isovolumetric relaxation time (IVRT), mitral annular e', TE-e', IVRT/TE-e', E/Vp, E/e', pulmonary vein flow parameters consisting of S, D, and S/D) were evaluated at baseline and 45 days after LAA closure.

RESULTS: The median age of the patients was 69 (54-78) years and 75% (n: 9) of them were male. All patients completed forty-five days of follow-up. Compared to the baseline values, E/Vp ratio and BNP levels (1.95 (0.94-3.32) *vs.* 2.37 (1.09-4.46), *p*= 0.015; 290.0 (90-1271) pg/ml *vs.* 322.00 (106-1635) pg/ml, *p*=0.018, respectively) increased, and pulmonary vein S wave and S/D ratio (0.67 (0.33-0.92) *vs.* 0.38 (0.23-0.91) m/sec, *p*=0.048; 1.62 (0.86-5.75) *vs.* 1.33 (0.11-3.35), *p*=0.019, respectively) decreased after LAA closure.

CONCLUSIONS: In the present study, we demonstrated that patients with AF have shown impaired diastolic functions and elevated BNP levels after the percutaneous closure of the LAA.

Key Words:
Percutaneous left atrial appendage closure, Ventricular diastolic dysfunction, Natriuretic peptide.

Introduction

Atrial fibrillation (AF) is a global health care problem with evidence suggesting an increasing prevalence and incidence worldwide[1]. The prevalence of AF is increasing with age, reaching up to 5% of patients older than 65 years, and is associated with 20%-30% of stroke episodes in that population[2]. Thrombus formation inside the left atrial appendage (LAA) is the most common cause of ischemic stroke in AF patients[3]. Although oral anticoagulant (OAC) is effective in reducing the incidence of ischemic stroke, it also increases the risk of hemorrhage complications in these patients[4]. Consequently, devices for percutaneous LAA closure have been developed as an alternative to OAC in patients at high risk for stroke with contraindications to OAC. On the other hand, LAA has several important mechanical and endocrine functions regarding unique anatomical and physiological properties. Because the LAA is a more distensible chamber than the left atrium (LA), it plays an important role as a decompression chamber for the LA and spares the LA from an acute rise in pressure. It has been previously shown that exclusion of the LAA may impair hemodynamic response to volume or pressure overload. Moreover, in experimental studies, it has been demonstrated that LAA elimination increases the mean dynamic stiffness constant of the LA diastolic pressure-volume relationship[5]. These studies suggested that reduced LA compliance after LAA closure may result in a larger increase in LA pressure and pulmonary vein stretch and endothelial dysfunction, thereby promoting the development of AF and thrombogenesis. Due to the close relationship between the mechanical

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and electrical dynamics of LA and left ventricular (LV) diastolic functions, it is inevitable to see changes in LV diastolic functions after LAA closure. However, it is not known whether changes in LA function after LAA closure affect the LV diastolic function. B-type natriuretic peptide (BNP) has been reported that BNP level is associated with LV diastolic dysfunction[6]. Therefore, in the present study, we aimed to non-invasively assess the impact of percutaneous LAA closure on LV diastolic functions with echocardiographic parameters and BNP levels in high-risk groups of patients with AF.

Patients and Methods

Study Patients

In this study a total of 15 patients with a history of paroxysmal or persistent AF for at least 6 months, CHA_2DS_2-VASc score ≥2 and contraindicated to oral anticoagulation were examined, and 12 patients were found to be eligible for the procedure (1 patient did not give consent to the procedure, 1 patient had a thrombus in the LAA, and 1 patient had a small LAA ostium diameter). Contraindications for OAC were mainly serious bleeding requiring hospitalization even at therapeutic anticoagulation levels (i.e., hemorrhagic stroke, hematuria, hemoptysis, lower or upper gastrointestinal bleeding, subcutaneous hematoma, and skin necrosis). Congenital heart disease, prosthetic heart valve, significant valvular heart disease, low CHA_2DS_2-VASc score, massive pericardial effusion or constriction, presence of LA thrombus, active infection, and severe atheromatous disease in the aortic arch were determined as exclusion criteria. The CHA_2DS_2-VASc score was calculated by assigning 1 point each for the presence of congestive heart failure (HF), hypertension, diabetes mellitus, age of 65 to 74 years, female sex, and vascular diseases and 2 points for age ≥75 years and a history of stroke. Congestive HF was defined as recent decompensated HF irrespective of LV ejection fraction or the presence of moderate-to-severe LV systolic dysfunction on cardiac imaging. Hypertension was defined as the previous use of antihypertensive medications, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as the use of antidiabetic agents or insulin in the patient's medical history or a fasting glucose level ≥126 mg/dL. Transient ischemic attack and systemic embolism were accepted as the equivalent risk factors for stroke. The presence of previous myocardial infarction, peripheral arterial disease, or complex aortic plaques has been accepted as a vascular disease. The acronym HAS-BLED represents each of the bleeding risk factors and assigns 1 point for the presence of each of the following: hypertension (uncontrolled systolic blood pressure >160 mm Hg), abnormal renal and/or liver function, previous stroke, bleeding history, or predisposition, labile international normalized ratios, elderly, and concomitant drugs and/or alcohol excess[7]. Blood samples for BNP levels were obtained from the patients before the procedure and at the follow-up visit. The Local Ethics Committee of Hacettepe University Hospital institution approved the study protocol (Decision No: LUT 12/66) and written informed consent was obtained from all the patients.

Procedure

Before the procedure, LAA size, morphology, and the absence of thrombus in LA and LAA were evaluated by transesophageal echocardiography (TEE). After the transseptal puncture, heparin was administered to achieve an activated clotting time of 200-300 sec. At least 2 standard projections (RAO cranial and RAO caudal) were performed to obtain good visualization of the LAA. Fluoroscopy and TEE imaging were used to re-evaluate the LAA and to select an appropriate device for each patient. The size of the WATCHMAN device (Boston Scientific, Natick, MA, USA) was chosen to be at least 20% larger than the measured diameter at the landing zone. TEE was used to check for the compression, positioning, stability of the device, peri-device leak, and the relationship between the device and adjacent structures. The patients were monitored for at least 6 hours with blood pressure and heart rate monitoring. Transthoracic echocardiography, electrocardiography, and chest X-ray were performed within 24 h after the procedure to rule out complications. The patient remained on warfarin (target internal normalized ratio: 2.0-3.0) plus low-dose aspirin for a minimum of 45 days following the procedure and continue taking aspirin daily indefinitely.

Echocardiographic Evaluation

Standard transthoracic echocardiography (TTE) was performed on all patients according to established clinical laboratory practice using the GE Vivid 5 system (GE Ultrasound; Horten, Norway) with a 2.5-3.5 MHz variable frequency transducer. Ten cardiac cycles were selected for measurements, and the results were averaged. LV end-diastolic diameter, end-systolic diameter, interventricular septum thickness, left ventricular posterior wall thickness, LA diameter was measured at parasternal long-axis view using M-mode. The Teichholz method was used to calculate LV ejection fraction. Pulse-wave doppler was used to measure peak early (E) mitral inflow velocities, the deceleration time of early mitral inflow velocity (DT), and the isovolumic relaxation time (IVRT). The tissue doppler imaging of the mitral annulus movement was obtained from the apical 4-chamber view. A 1.5-mm sample volume was placed sequentially at the lateral and septal annular sites to measure e' velocity and the E/e' ratio was then calculated. The color M-mode flow propagation velocity (Vp) was measured as the slope of the first aliasing velocity during early filling from the mitral valve plane to 4 cm distally into the LV cavity. LA volumes (mL) were measured in the apical four-chamber view by using the area length method. The maximal LA volume was obtained before mitral valve opening and the minimal volume before valve closure. LA emptying fraction was derived as the difference between volumes divided by the maximal volume. TE-e' was defined as the time interval between the peak of R wave in QRS complex and onset of mitral E velocity is subtracted from the time interval between QRS complex and onset of e' velocity. Pulmonary vein pulse-wave doppler signals (D and S wave) were acquired in the apical 4-chamber view by interrogating the right upper pulmonary vein. The deceleration time of the D wave (PVDT) was measured as the time interval between peak velocity and the upper deceleration slope extrapolated to zero.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS Inc., Armonk, NY, USA). Since the study population consisted of 12 patients and the numerical variables did not exhibit normal distribution, values were shown as median (minimum-maximum). Differences in diastolic functions and BNP levels after the procedure were examined using the Wilcoxon Signed-Rank Test. The relationship between changes of the parameters found to be significant as a result of the test was analyzed using Spearman Correlation Analysis. The accepted Type I error was 5% in this study.

Results

The median age of 12 patients with successful LAA closure was 69 (54-78) years. Nine of the 12 patients (75%) were male, 8 patients had permanent AF (66.7%) and the others had paroxysmal AF (33.3%). AF duration of all patients was longer than one year. The rhythm in all patients was AF at the time of echocardiographic examination. It was detected that heart failure in 5 patients (41.7%), vascular disease in 5 (41.7%), liver or kidney disease in 2 (16.7%), diabetes mellitus in 1 (8.3%), hypertension in 12 (100%), drug or alcohol use in 4 (33.3%), history of stroke was detected in 4 (33.3%). The median CHA_2DS_2-VASc and HAS-BLED score were 3.5 (2-6) and 4.0 (3.0-6.0), respectively. Demographic and clinical findings are shown in Table I.

Percutaneous closure of LAA was successfully performed in all patients. The mean LAA ostium diameter measured by TEE was found to be 20.4 ± 3.8 mm. The median implanted device size was 24.6 (21-30) mm. The mean procedure time was 58.6 (50-75) minutes, and the mean fluoroscopy time was 19.1 (12-30) minutes. The average hospital stay was 2 (1-4) days. No major adverse events such as procedure-related death, new stroke, systemic embolism, significant residual peri-device leak, pericardial tamponade, and bleeding requiring transfusion were observed. One patient (8.3%) had a hematoma at the vascular access site and resolved spontaneously during follow-up. Minimal pericardial effusion was observed in one patient (8.3%). All patients were followed for at least 600 days. No major adverse events associated with LAA closure (death, new stroke, systemic embolism, pericardial tamponade, or bleeding requiring transfusion) were observed in any patient during this period. Pulmonary venous obstruction or thrombus formation on the device was not detected in any patient on TEE performed on the 45th day. At the same time, trivial peri-device leaks were observed in 2 patients (16.7%).

There was no change in the LV diameters and systolic functions of the patients at the end of the follow-up period [LV ejection fraction, 54 (32-67)%; LV end-diastolic diameter (5.35 (4.2-6.8) cm; LV end-systolic diameter (3.59 (2.52-5.61) cm]. There was no significant difference in structural and functional change of LA. The baseline emptying fraction of LA in the study population was not significantly different after 45 days [31.50% (10-49) *vs*. 29.50% (20-48), p=0.723]. In

Table I. Baseline characteristics of study population.

	Median	Min-Max	N (%)
Age (years)	69,00	54-78	–
65 ≤ Age > 75	–	–	7 (58.3)
Age ≥ 75	–	–	3 (25.0)
Sex			
Female	–	–	3 (25.0)
Male	–	–	9 (75.0)
AF Type			
Paroxysmal	–	–	4 (33.3)
Permanent	–	–	8 (66.7)
İndication for LAA closure			
Bleeding	–	–	10 (83.3)
Thrombotic event	–	–	-2 (16.7)
Heart Failure	–	–	5 (41.7)
Vascular disease	–	–	5 (41.7)
Liver or Kidney dysfunction	–	–	2 (16.7)
Diabetes mellitus	–	–	1 (8.3)
HT	–	–	12 (100)
Stroke	–	–	4 (33.3)
Bleeding	–	–	10 (83.3)
Drug-alcohol	–	–	4 (33.3)
CHADS2-VASc Score	3,50	2-6	–
HASBLED Score	4,00	3,0-6,0	–
HASBLED Risk Level			
Low (0 < HASBLED Score < 2)	–	–	–
İntermediate (2 < HASBLED Score < 3)	–	–	–
High (HASBLED Score ≥ 3)	–	–	12 (100)

the TTE assessment, no significant difference in diastolic function parameters was observed in the overall population between baseline and follow-up, except for E/Vp ratio which increased after LAA closure [1.95 (0.94-3.32) *vs.* 2.37 (1.09-4.46), p=0.015), pulmonary vein S wave and S/D ratio which decreased after LAA closure (0.67 (0.33-0.92) *vs.* 0.38 (0.23-0.91) m/sec, p=0.048; 1.62 (0.86-5.75) *vs.* 1.33 (0.11-3.35), p=0.019, respectively] (Table II).

Median BNP concentration increased 45 days after the procedure from 290.0 (90-1271) pg/ml to 322.00 (106-1635) pg/ml (p=0.018). Although these diastolic function parameters did not correlate significantly with each other, it was found that BNP levels correlated with regarding delta values of E/Vp, S/D ratio (Table III).

Discussion

In our study, we showed that percutaneous closure of LAA negatively affected important echocardiographic markers representing diastolic functions and caused a significant increase in the levels of BNP. In addition, we found that there was a significant correlation between the increase in BNP levels and changes in these diastolic function parameters.

Percutaneous LAA closure is sometimes the only option for ischemic stroke prevention, especially in AF patients with contraindication for long-term OAC or high risk of bleeding. Although the safety and efficacy of this procedure have been demonstrated in randomized controlled trials, the data about the impacts of LAA closure on diastolic function are not well established[4,8,9].

In recent years, several studies[10] have been done on the relationship between transmitral and pulmonary vein velocities and LV diastolic pressures. In patients with AF, the A wave is absent from both mitral and pulmonary flow velocities and, therefore, one cannot apply the ratio of early filling to late filling velocity (E/A ratio), atrial filling fraction, or the pulmonary retrograde A velocity in the estimation of filling pressures[11]. In this situation, doppler measurements that can be applied include mitral E velocity, DT, IVRT, DT of pulmonary venous diastolic velocity. In addition to such routine parameters, Vp, mitral annular e', TE-e', E/Vp, E/e', IVRT/ TE-e', S/D ratio can be used.

Table II. Impact of procedure on diastolic functions and BNP levels.

Variables	Pre procedure	Post procedure	*p*-value
LA Dimeter	4.30 3.2-5.6	4.10 3.2-5.3	0.372
E	0.95 0.44-1.36	0.94 0.44-1.25	0.859
DT	167.30 67.7-386.0	173.85 97.0-289.7	0.695
IVRT	112.50 66.0-197.0	115.40 64.7-179.0	0.374
$T_{E-e'}$	45.00 24-83	40.50 11-78	0.638
Vp	0.43 0.31-0.55	0.43 0.15-0.47	0.108
LA max	80.42 42.55-194.1	87.20 33.0-137.0	0.875
LA min	55.00 22-175	62.00 17.0-116	0.432
LAEF	31.50 10-49	29.50 2-48	0.723
IVRT/ T E-e’	2.23 1.27-4.34	2.75 0.83-9.09	0.814
E/VP	**1.95** **0.94-3.32**	**2.37** **1.09-4.46**	**0.015***
E/e’ Septal	16 8-21	13 9-19	0.583
E/e’ Lateral	11 5-16	9.6 5-14	0.583
S/D	**1.62** **0.86-5.75**	**1.33** **0.11-3.35**	**0.019***
PVS	**0.67** **0.33-0.92**	**0.38** **0.23-0.91**	**0.048***
PVD	0.32 0.16-0.50	0.35 0.12-2.44	0.875
PVDT	195.50 85.2-310.0	211.20 122.7-326.0	0.433
BNP	**290.0** **90-1271**	**322.00** **106-1635**	**0.018***

*Statistical Comparison Before and After the Procedure Analyzed with Wilcoxon Signed Rank Test. $p < 0.05$ was accepted as statistically significant.

There is no comprehensive information in the literature regarding the effects of diastolic echocardiographic parameters after percutaneous closure of LAA in patients with AF. There are several experimental studies demonstrating that LAA occlusion may not significantly impair

Table III. Correlation of parameters that differ after procedure.

Variables	PVS %		S/D %		E/VP %		BNP %	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
PVS %	–	–	0.491	0.105	0.100	0.758	-0.036	0.911
S/D %	0.491	0.105	–	–	-0.352	0.262	**-0.586**	**0.045***
E/VP %	0.100	0.758	-0.352	0.262	–	–	**0.598**	**0.040***
BNP %	-0.036	0.911	**-0.586**	**0.045***	**0.598**	**0.040***	–	–

*Spearman Correlation Analysis was used in evaluation of the relationship between diastolic functions and BNP level, $p < 0.05$ was accepted as statistically significant. ***r***: Power of Correlation Relationship.

LA function and does not lead to harmful atrial remodeling or loss of contractile function[12,13]. The fact that measurements were made in sinus rhythm and the LAA was surgically closed in all these animal studies does not reflect clinical practice. S wave, D wave, and DT of D wave can be measured with doppler of pulmonary vein flow in patients with AF. In our study, a significant decrease was found in pulmonary vein S-wave and S/D ratio. Significant changes in these parameters, which are specific markers of diastolic dysfunction in patients with AF, support that the diastolic functions of LA and LV are affected after percutaneous LAA closure. LAA is more compliant than the LA main chamber and plays an important role in the presence of LA pressure and/or volume overload[14]. The separation between LAA and LA after complete endothelialization of the device results in the disappearance of this LAA reservoir function[15]. In our study, it was thought that significant changes in specific echocardiographic parameters reflecting the diastolic dysfunction developed with this mechanism in the early postoperative period.

BNP, a marker of neurohormonal activation secreted by cardiomyocytes in response to ventricular wall stretch, has a basic role in cardiovascular remodeling and volume homeostasis[16]. It was shown that plasma BNP values were closely related to the diastolic functional status in patients with stable HF[17]. Although LAA closure is known to affect LA functions, its effect on LV functions has been less studied[18]. Lubien et al[19] shown that a BNP value of 62 pg/mL had a sensitivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction. In our study, the higher BNP levels during the follow-up compared to baseline indicates that there is also a deterioration in LV functions. Because the major source of plasma BNP is cardiac ventricles, and this suggests that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides[19]. In our study, the significant correlation between BNP levels and specific markers of diastolic dysfunction (i.e., E/Vp and S/D) supports the development of diastolic dysfunction in the LV.

Our study has some important limitations. First, this was a single-center study, and the number of patients is relatively limited. Observed changes may be caused by chance in this small study cohort. Another limitation of the study is the lack of invasive hemodynamic measurements. However, the fact that TTE and TEE safely reflect hemodynamic data has currently limited the need for invasive evaluation. Since it is possible to evaluate LA and LAA more comprehensively with the 3D echocardiography, the inability to use this method in our study is among the other limitations. To understand how diastolic function parameters, which we examined in the early postoperative period in our study, will progress in the long term, there is a need for studies with a larger number of patients and a longer follow-up period. Finally, just like any other biomarker, BNP levels may also vary on a daily basis. As blood samples were obtained only at two-time points, some information on the time course of this marker may have been missed.

Conclusions

In our study, it was found that LAA closure in patients with AF who have contraindications to OAC has negative effects on LV diastolic functions. To determine how this effect is reflected in clinical practice, further studies with a larger number of patients, assessing functional capacity, and clinical endpoints are required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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