Original Article
The influence of left atrial appendage closure on the structure and function of the left atrium

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Abstract: Objectives: We aimed to investigate the influence of left atrial appendage closure (LAAC) on the structure and function of the left atrium (LA). Methods: The study included 67 consecutive patients with non-valvular atrial fibrillation (NVAF) who had undergone percutaneous LAAC using the Watchman device. The size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA were determined before LAAC, 48 h after LAAC, and at the first follow-up (45-60 days) using echocardiography. Additionally, the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured before LAAC; 6 h, 24 h, and 48 h after LAAC; and at the first follow-up (45-60 days). Results: LAAC was successfully performed in the 67 patients. The end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA were significantly lower at 48 h after LAAC and at the first follow-up (45-60 days) than before LAAC. Additionally, the size of the LA was significantly lower at 48 h after LAAC than before LAAC. Moreover, the NT-proBNP levels were significantly higher at 6 h and 24 h after LAAC than before LAAC (P < 0.01 and P = 0.013, respectively). However, the NT-proBNP levels before and 48 h after LAAC did not differ significantly (P = 0.26), and the NT-proBNP levels were significantly lower at the first follow-up (45-60 days) than before LAAC (P < 0.01). Conclusion: In conclusion, LAAC might cause reductions in the size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA, and variations in plasma BNP levels at different time points.

Keywords: Brain natriuretic peptide, left atrial appendage, atrial fibrillation, left atrium, watchman device

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice [1]. It has been shown to increase the risk of ischemic stroke [2] and has been reported to be an underlying factor in up to 20% of stroke cases among elderly patients [3]. Left atrial appendage closure (LAAC) has been investigated as an alternative treatment for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) [4-8], and its safety and efficacy have been shown previously [5]. However, it is unknown whether LAAC has any significant pathophysiological implications. The left atrial appendage (LAA) plays a role in the release of brain natriuretic peptide (BNP). In response to pressure overload and ventricular volume expansion, BNP is secreted by cardiomyocytes [9]. Previous studies have demonstrated that BNP levels were higher in patients with AF than health people, and that the levels significantly

decreased after recovering to sinus rhythm [10]. The N-terminal pro-brain natriuretic peptide (NT-proBNP) is an N-terminal fragment without activity that is produced after the release of BNP. The half-life of NT-proBNP is longer than that of BNP, and the former one is more stable. What's more, its concentration can reflect the synthesis of BNP in a short time. Limited information is available on the influence of LAAC on NT-proBNP levels. Additionally, the influence of LAAC on the structure of the left atrium (LA) is unclear. Therefore, in the present study, we aimed to investigate the influence of LAAC on the structure and function of the LA.

Materials and methods

Study population

The study included 67 consecutive patients with NVAF who had undergone percutaneous
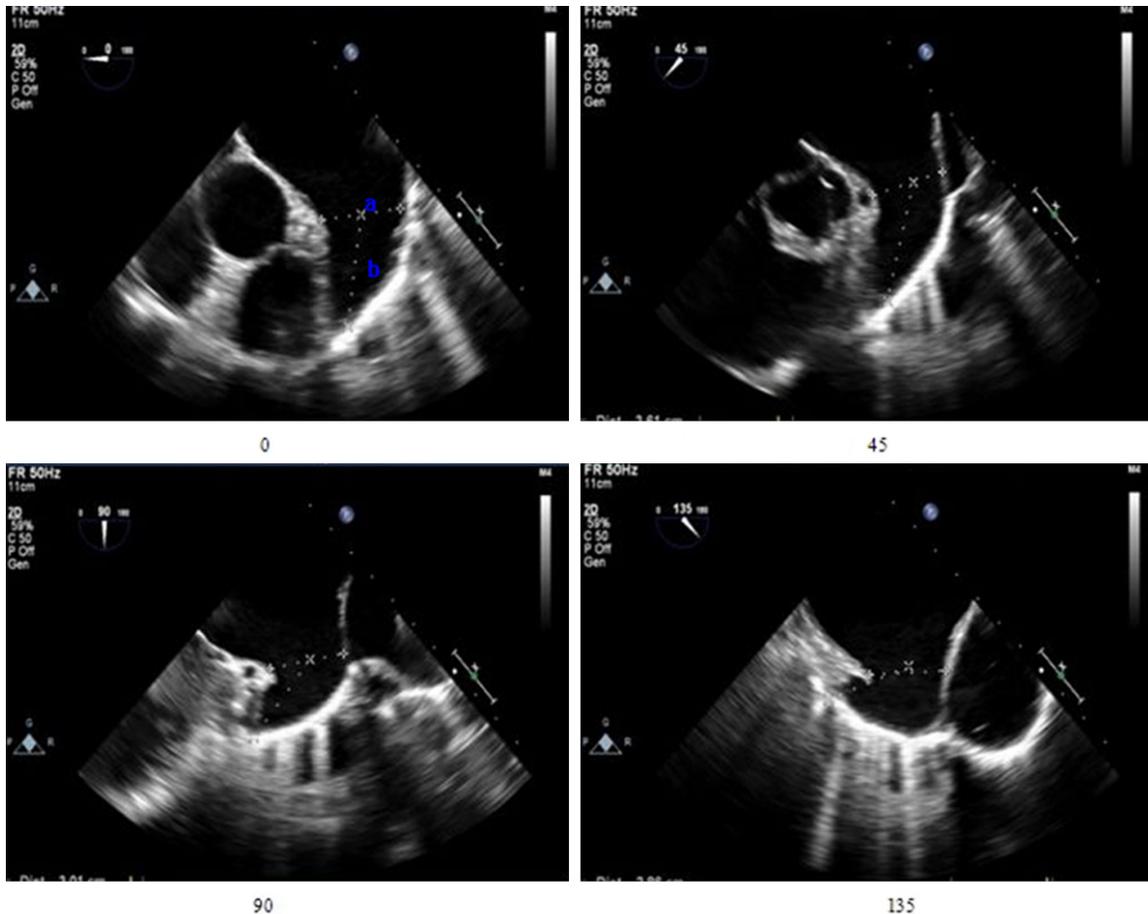
Figure 1. Measurements of the left atrial appendage (LAA) orifice width and depth from 0°, 45°, 90°, and 135° by transesophageal echocardiography (a indicates LAA orifice width, b indicates LAA depth).

LAAC at our center between September 2014 and January 2016. All patients underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) to evaluate the presence of an intra-cardiac thrombus and determine the structure of the heart. This study was approved by the ethics committee of Southwest Hospital, and all patients were provided written informed consent prior to LAAC. The inclusion criteria were as follows: (1) presence of NVAF; (2) high risk of bleeding as assessed with the HAS-BLED score; (3) CHA2DS2 score > 2; and (4) contraindication for oral warfarin or unwilling to use warfarin over a long period. The exclusion criteria were as follows: (1) preoperative TEE showing suspicious or clear thrombosis; (2) AF with cardiac valve disease; (3) serious heart failure (NYHA class IV); (4) acute myocardial infarction; and (5) liver and kidney dysfunction.

NT-proBNP measurement

Plasma samples were collected using disposable tubes, and immediately centrifuged at 41°C. The plasma was then frozen and stored at 4°C. Plasma NT-proBNP levels were measured using the Roche BNP Immunoassay kit (Roche Diagnostics, USA). Plasma NT-proBNP levels were measured before LAAC; 6 h, 24 h, and 48 h after LAAC; and at the first follow-up after discharge (45-60 days).

TTE and TEE

All patients underwent TTE and TEE. TEE was performed using a 3-dimensional TTE system. According to previously published methods, TEE was performed to determine whether there was any LAA thrombosis during the application of different angles (0°, 45°, 90°, and 135°) to measure the maximum orifice size and depth of

Table 1. Patient characteristics

Patient characteristics	All (n = 67)
Sex	Male (46.8%)
Age (year)	67.6±8.1
Hypertension	52%
Diabetes	19.3%
Stroke	30.2%
BMI	22.8±5.1
CHA2DS2VASc score	4.2±1.3
HASBLED score	2.4±0.9

the LAA [11] (**Figure 1**). Prior to TEE, all patients signed an informed consent form. Lidocaine hydrochloride was administered at the throat to anesthetize the posterior pharynx and tongue. The size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA were detected using TTE before LAAC, 48 h after LAAC, and at the first follow-up after discharge (45-60 days). Additionally, the LAA was checked for thrombi and its 3-dimensional structure was assessed using TEE.

Catheterization and closure procedure

All patients underwent cardiac catheterization and LAAC via the right femoral vein. After general anesthesia, the pressures of the pulmonary artery, right ventricle, right atrium, and LA were assessed during catheterization. LAA angiography was used to assess the shape of the LAA. The Watchman device (Atritech, Plymouth, MN, USA) was used for closure. According to the depth and width of the LAA, we selected the device size. The diameter of the device was approximately 20% larger than the diameter of the LAA to prevent device displacement and migration. On TEE and LAA angiography, we identified the position of the device, and ensured that it was in a fixed position. We then completely released the device.

Statistical analysis

All data are presented as means ± standard errors. The repeated measures analysis of variance was used to evaluate the size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA; size of the right atrium; and NT-proBNP levels at the different time points. All statistical analyses were performed using SPSS software (version 13.0; IBM Corp., Armonk, NY, USA). Differences

were considered statistically significant when the *P*-value was < 0.05.

Results

Patient and procedural characteristics

The patient characteristics are summarized in **Table 1**. LAAC was successfully performed in the 67 study patients, without any operative complications. The sizes of the devices used in the patients ranged from 21 to 33 mm. A minor residual shunt (blood flow velocity < 4 mm on color Doppler) was noted in 8 patients, and the shunt disappeared at 48 h after LAAC in 6 of these patients and at 45-60 days after LAAC in the other 2 patients. All patients underwent TTE at 48 h after LAAC.

Follow-up

All the patients completed the first follow-up (45-60 days). TTE, TEE, and NT-proBNP measurements were performed. No complications were noted at the follow-up.

TTE and cardiac catheterization

The size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA, and the size of the right atrium before LAAC, 48 h after LAAC, and at the first follow up (45-60 days) are presented in **Table 2**. The end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA were significantly lower at 48 h after LAAC and at the first follow-up (45-60 days) than before LAAC. Additionally, the size of the LA was significantly lower at 48 h after LAAC than before LAAC; however, the size of the LA before LAAC and at the first follow-up (45-60 days) did not differ significantly. The mean pressures of the pulmonary artery, right ventricle, right atrium, and LA are presented in **Table 3**.

NT-proBNP levels

The NT-proBNP levels before LAAC; 6 h, 24 h, and 48 h after LAAC; and at the first follow-up (45-60 days) are presented in **Figure 2**. The NT-proBNP levels were significantly higher at 6 h and 24 h after LAAC than before LAAC (1464.6 pg/mL vs. 850.6 pg/mL, P < 0.01 and 1075.2 pg/mL vs. 850.6 pg/mL, P = 0.013, respectively). However, the NT-proBNP levels before and 48 h after LAAC did not differ signifi-

Table 2. Echocardiographic data of the size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the left atrium; size of the right atrium

Echocardiograph	0	48 h	45-60 d
LA size (mm)	45.8±5.6	44.1±5.8 (P < 0.01)	45.5±5.9 (P = 0.25)
RA size (mm)	44.7±6.6	44.2±5.9 (P = 0.20)	44.4±5.5 (P = 0.32)
LA end-diastolicvolume (ml)	63.5±22.9	60.9±19.6 (P = 0.004)	61.9±19.7 (P = 0.02)
LA end-systolic volume (ml)	93.6±28.7	86.1±28.7 (P < 0.01)	88.9±28.5 (P < 0.01)
LA end-diastolic area (cm^2)	23.0±3.8	21.8±3.6 (P = 0.02)	22.0±3.7 (P = 0.04)
LA end-systolic area (cm^2)	27.7±5.1	26.2±4.7 (P < 0.01)	26.4±4.9 (P = 0.002)

LA: left atrium; RA = right atrium.

Table 3. Results of cardiac catheterization

Mean pressure	Pre-operation (mmHg)	Post-operation
LA	15.8±1.8	15.9±1.9
RA	10.1±3.2	
RV	18.1±4.7	
PA	22.3±5.7	

LA = left atrium; RA = right atrium; RV = right ventricle; PA = pulmonary artery.
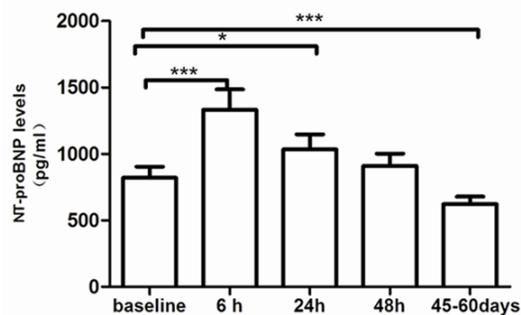

Figure 2. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels before left atrial appendage closure (LAAC); 6 h, 24 h, and 48 h after LAAC; and at the first follow-up (45-60 days). ***P < 0.01 baseline vs. 6 h; baseline vs. 45-60 days after LAAC. *P = 0.013 baseline vs. 24 h.

cantly (850.6 pg/mL vs. 904.5 pg/mL, P = 0.26), and the NT-proBNP levels were significantly lower at the first follow-up (45-60 days) than before LAAC (705.1 pg/mL vs. 850.6 pg/mL, P < 0.01).

Discussion

The present study found that the NT-proBNP levels were significantly higher at 6 h and 24 h after LAAC than before LAAC and were significantly lower at the first follow-up (45-60 days) than before LAAC, and that the NT-proBNP levels before and 48 h after LAAC were not different. Additionally, the study found that the

end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA were significantly lower at 48 h after LAAC and at the first follow-up (45-60 days) than before LAAC. Furthermore, the study found that the size of the LA was significantly lower at 48 h after LAAC than before LAAC, and that the size of the LA before LAAC and at the first follow-up (45-60 days) was not different.

The LAA originates from the main body of the LA [12]. It is the most common site of cardiac thrombus formation in patients with NVAF, and more than 90% of all thrombi in the LA have been reported to originate in the LAA [13]. During sinus rhythm, the LAA has normal contraction function and adequate blood flow, preventing thrombus formation inside its cavity. However, during AF there is a decrease in LAA contractility and function with Doppler velocities and dilation of the LAA [14, 15], which increase the risk of thrombus formation inside its cavity. Percutaneous LAAC is an alternative therapy to prevent thromboembolic events in patients with NVAF [16, 17], and its safety and efficacy have been shown previously [4]. To the best of our knowledge, the present study is the first to evaluate variations in the structure of the LA and NT-proBNP levels at various time points after LAAC.

Recently, it was reported that the size of the LA could positively predict cardiac risk, including the recurrence of AF, heart failure, myocardial infarction, and other such conditions [18, 19]. Gupta DK demonstrated that abnormalities in the structure and function of the LA increased the incidence of AF and were associated with a high risk of stroke [20]. Additionally, a reduction in the size of the LA was found to increase blood flow velocity in the LA and reduce the likelihood of thrombus formation [21]. Therefore, we believe that reductions in the

size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA could influence the structure and function of the LA and help improve cardiac function.

NT-proBNP is an important natriuretic hormone. The LAA plays an important role in the secretion of NT-proBNP. Additionally, it plays an important role in regulating intravascular volume and hemodynamics. A previous study showed that high plasma NT-proBNP levels were correlated positively with the risk of thromboembolic complications with AF [22]. In LAA dysfunction, elevated NT-proBNP levels, especially in patients with NVAF, have been shown to be associated with a prothrombotic state [23]. Thus, NT-proBNP is a useful marker for the risk stratification of stroke in patients with NVAF [24].

Schwartz [25] found that endothelial cells covered the Watchman device and firmly attached the device to the interface of the LA at 45 days after discharge. Kar [26] observed that the surface of the Watchman device was completely incorporated with organizing neo-endocardial growth, involving well-organized granulation tissue with only minimal fibrin deposition, at 28 days. We believe that BNP levels will further decrease over time owing to advanced endothelialization of the device surface after complete occlusion of the LAA, and this may explain our results that NT-proBNP levels were lower at 45-60 days after LAAC than immediately after LAAC.

The NT-proBNP levels were significantly higher at 6 h and 24 h after LAAC than before LAAC. Several factors may have contributed to these results. First, contrast media injection during LAA angiography might have stimulated BNP secretion. Second, stretching of the LAA by the closure device during the procedure might have stimulated BNP secretion. Finally, procedural stress might have stimulated BNP secretion. However, the potential pathophysiological mechanisms for the variations in NT-proBNP levels are unknown. Therefore, further studies and longer follow-up are required to determine the long-term progression of the neurohormonal response after LAAC.

Limitations

The present study has some limitations. Patients with serious heart failure and acute myocardial infarction were excluded; however, other factors that were not included in the exclusion criteria might have influenced the NT-proBNP levels.

Conclusion

LAAC might cause reductions in the size, end-diastolic volume, end-systolic volume, end-diastolic area, and end-systolic area of the LA, and variations in plasma BNP levels at different time points. These findings indicate a loss of neurohormonal function and variations in the structure of the LA in the short-term follow-up period after LAAC.

Disclosure of conflict of interest

None.

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