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Original Article

The Effect of Minimally Invasive Thoracoscopic Left Atrial Appendage Excision on Cardiac Dynamic and Endocrine Function

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Purpose: Left atrial appendage (LAA) isolation is an effective surgical treatment for decreasing thromboembolic risk. We sought to evaluate the short-term effect of minimally invasive surgery with LAA excision on left atrial dynamic and endocrine function in atrial fibrillation (AF) patients.

Methods: A total of 52 patients with paroxysmal AF undergoing minimally invasive surgery with LAA excision in Anzhen Hospital from October 2012 to June 2014 were enrolled in the study. The natriuretic peptide plasma level was determined by enzyme-linked immunosorbent assay (ELISA), and left atrial dynamic function was measured preprocedure by real-time three-dimensional echocardiography and postprocedure after 7 days and 3 months.

Results: With the exception of six recurrences, 88.5% (46/52) of the patients were prospectively followed over 3 months in terms of their sinus rhythm postprocedure. No severe operative complications or embolism events occurred within those 3 months. Echocardiography showed a 3–6% decrease in left atrial volume postprocedure, and dynamic function was largely restored by 3 months. There was no significant change in natriuretic peptide levels, although a slight decrease was detected 7 days postprocedure, which gradually recovered by 3 months (*P* = 0.350).

Conclusions: There are no significant differences in left atrial dynamics and natriuretic peptide secretion in AF patients after minimally invasive surgery with LAA excision.

Keywords: atrial fibrillation, left atrial appendage, atrial natriuretic peptide, atrial function

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Introduction

As the most common sustained cardiac arrhythmia, atrial fibrillation (AF) is affecting around 1–2% of the global population, more than 33 million worldwide.[1,2] For many years, intensive research into AF has provided deep insight into the subject while elucidating more knowledge gaps and inadequacies in the current therapeutic options.[3–6] Specifically, the advances in widely adapted catheter ablation technologies have not converted to significant gains in success rates over recent years.[7] It is however important to note that stroke is the most dreaded complication for each AF patient. Therefore, selection of the best strategy aiming at lowering the risk of embolic events is becoming more problematic. The left atrial appendage (LAA) is considered a major source of thromboembolic origin in AF patients.[3] However, some studies have shown that LAA contractile function contributes greatly to left atrial mechanical contraction.[8–10] Moreover, the LAA also plays an important role in body fluid regulation via the secretion of atrial natriuretic peptide (ANP).[11] It is not enough to believe that LAA elimination should be applied indiscriminately.[12,13] More recently, the safety and efficacy of surgical ablation with LAA excision have been reported in AF patients with medium-term follow-up after using different devices and methodologies.[8,14–16] However, few studies have comprehensively evaluated the effect of minimally invasive surgery with LAA excision on left atrial dynamics and endocrine function to date.

Patients and Methods

Patient selection

A total of 52 patients with paroxysmal AF who underwent minimally invasive surgery with LAA excision in Anzhen Hospital between October 2012 and June 2014 were enrolled in the study. The inclusion criteria were paroxysmal AF defined according to the 2012 HRS/EHRA/ECAS expert consensus statement on AF. Paroxysmal AF is defined as recurrent AF (two episodes) that terminates spontaneously within 7 days, and episodes of AF lasting 48 hours that are terminated with electrical or pharmacologic cardioversion are classified as paroxysmal AF episodes.[17] The inclusion criteria further included a left ventricular ejection fraction of more than 50% with ultrasonic cardiography (UCG) evaluation; the absence of LAA thrombus on transesophageal echocardiography (TEE); and the refusal of catheter ablation after more than one instance where antiarrhythmic drugs were ineffective or intolerable. The exclusion criteria were persistent AF/longstanding persistent AF; a left atrial dimension of greater than 60 mm; patients with organic heart disease, for example, valvular heart disease, cardiomyopathy, and coronary artery disease; secondary AF; severe pleural adhesions; and recurrence during follow-up.

The baseline characteristics of the patients are listed in **Table 1**. These patients comprised 30 male and 16 female patients, and their ages ranged from 31 to 73 years, with an average age of 60.9±10.6 years. In terms of the most common comorbidity, 25 (54.35%) patients had a history of hypertension, followed by diabetes (17.39%) and prior stroke (2.17%). The mean score of CHA2DS2-VASc for the enrolled patients was 1.48 ± 0.91, and none of the patients had undergone regular anticoagulation therapy despite their condition. All of the participants signed an informed consent form before participation. This study was approved by the Ethical Committees of Anzhen Hospital and Capital Medical University, Beijing, China.

Preoperative management

The preoperative evaluation included a baseline 12-lead electrocardiography (ECG) analysis; a chest radiograph; transthoracic UCG and TEE analyses; or coronary angiographic analysis (>45 years old) on admission. Daily respiratory function exercise was also recommended to effectively reduce postoperative pulmonary complications. All patients were required to fill out medical questionnaires about their AF history, CHA2DS2-VASc score, antiarrhythmic drug use, anticoagulant drug use, stroke/transient ischemic attack (TIA)/thromboembolism history, and so on.

Detection of ANP level

From each patient, 2 mL venous blood was collected in aprotinin tubes containing ethylenediaminetetraacetic acid, centrifuged at 3000 rpm for 10 minutes at 4 °C to separate the plasma, and stored in a cryogenic refrigerator at -80°C. An enzyme-linked immunosorbent assay (ELISA) was performed to detect the plasma levels of ANP. The assay was performed using the NPPA (Human/Mouse/Rat) ELISA (cat. no. KA1680; Abnova Corporation, Taipei, Taiwan) kit. Briefly, 100 µl anti-ANP polyclonal antibody was added to each well, and incubation occurred for 1.5 h at 37 °C. Next, 100 µl of standards, the samples to be tested, and the positive controls were added into the appropriate wells, which were precoated with anti-rabbit secondary antibody. The microplates were then incubated at 37 °C for 2.5 h, followed by the addition of 100 µl prepared streptavidin solution to each well and incubation at 37 °C for 45 min. Subsequently, 100 µl TMB one-step substrate reagent was added to each well, and incubation occurred at 37 °C for 30 min. Finally, the stop solution was added, and the optical density was immediately read at 450 nm on a microplate reader (Synergy4, BioTek, Winooski, VT, USA). All the measurements were performed in duplicate.

Surgical techniques

The surgical procedure was performed as previously described,[14,15] including epicardial radiofrequency

Table 1 Baseline characteristics of the patients

Characteristics	Results
Age (years)	60.9 ± 10.6
Male, n (%)	30 (65.22%)
Echocardiography	
LA size, mm	38.57 ± 5.76
LVEF, %	61.54 ± 4.91
Congestive heart failure	0
Hypertension, n (%)	25 (54.35%)
Diabetes, n (%)	8 (17.39%)
Stroke/TIA, n (%)	1(2.17%)
Vascular disease	0
CHA2DS2-VASc	1.48 ± 0.91

LA: left atrial; LVEF: left ventricular ejection fraction; TIA: transient ischemic attack

isolation of the bilateral pulmonary vein, ligament of Marshall resection, and excision of the LAA. After patients received general anesthesia with the double-lumen tube for one-lung ventilation, the operation started at the right chest site in the left lateral decubitus position. Two lateral 10 mm incisions were made in the sixth intercostal space (ICS) approximately 1 cm anterior to the midaxillary line for the thoracoscope port and dissector use port. A 5 cm right external thoracic incision at the third ICS between the anterior and midaxillary lines was made for the working port. After opening the pericardium 1 cm anterior and parallel to the phrenic nerve, the anatomic structures, such as the right superior pulmonary vein, right inferior pulmonary vein, inferior vena cava, and right pulmonary artery, were identified. Then, the pulmonary vein dissection was achieved using a Wolf Lumitip Dissector (AtriCure, West Chester, OH, USA), and the lower jaw of the Isolator Transpolar ENDO ablation clamp (AtriCure) with the red rubber catheter attached to the dissector tip was clipped. After the isolator jaws were clamped over the atrial cuff, the repetitive ablation procedure was initiated at most 5 times, with a 2 mm distance among each lesion moving toward the atrial cuff. Again, to check the effectiveness of the ablation, sensing and pacing (Detect and Carelink 2090 programmer; Medtronic, Minneapolis, MN, USA) were performed. Then, ganglionic plexi activity was detected before and after radiofrequency application. Finally, a 20F chest tube was placed through the incision of the thoracoscope port. After the right lung reinflated, the left-side procedures were initiated in a way similar to the right-side procedures, for example, the incision, electrophysiologic, dissection, and ablation procedures. The only difference between the left procedure and the right procedure was that the pericardium was opened 1 cm posterior and parallel to the phrenic nerve, and the ligament of Marshall was separated under direct vision. The LAA was then removed using an EZ-45G Endostapler (Johnson and Johnson Medical, Inc, Arlington, TX, USA) after the left pulmonary vein had been isolated. At the end of the procedure, a 20F drainage tube was inserted, and the incisions were closed.

Assessment of Left atrial function

Echocardiographic evaluation was performed using a Philips iE33 ultrasound system (Philips, Andover, MA, USA) and an S5-1/X3-1(2.0-3.5/1-3 MHz) transducer preprocedure as well as postprocedure after 7 days and 3 months. The following two-/three-dimensional measurements of the left atrial volume and the function indices were acquired for each subject: left atrial anteroposterior diameter (LAAPd), transmitral late diastolic filling velocity (A), left atrial maximum volume (LAV_{max}), left atrial preatrial contraction volume (LAV_p), and left atrial minimal volume (LAV_{min}). Left atrial ejection fraction (LAEF) was calculated using the following formula[18]: $(LAV_{max}\text{-}LAV_{min})/LAV_{max}$; left atrial active ejection fraction (LAAEF) was obtained with the following formula: $(LAV_p\text{-}LAV_{min})/LAV_p$; and left atrial passive ejection fraction (LAPEF) was achieved with the following formula: $(LAV_{max}\text{-}LAV_p)/LAV_{max}$. We followed the standards of the American Society of Echocardiography for the measurements made from two-/three-dimensional quantification echocardiograms.[19,20] LAAPd was obtained at left ventricular end systole as its largest diameter with the long axis plane of the left ventricle confirmed by two-dimensional echocardiography. Late transmitral velocity was assessed using pulsed wave Doppler in the apical four-chamber view. LAV_{max} was assessed at the end-ECG T wave before the opening of the mitral valve, whereas LAV_{min} was obtained at the peak of the R wave of the late diastolic left ventriculus. LAV_p was assessed at the precise beginning of the ECG P wave. The images were transferred to a separate workstation and analyzed using QLAB10.0 quantification software (Philips Medical Systems, Amsterdam, Netherlands).

Follow-up

All patients received the following drug treatment after surgery: 400 mg/day of amiodarone during the first postoperative month and 200 mg/day of amiodarone for the next two months. Postoperative anticoagulation (warfarin or aspirin) was administered based on the patients' CHA2DS2-VASc. Clinical status, laboratory examinations, 12-lead ECG analyses, 24-hour Holter monitoring, and transthoracic UCG were evaluated at 7 days and 3 months (10 days after the discontinuation of amiodarone) following the ablation. ECG examinations and 24-hour Holter monitoring (Del Mar Reynolds Medical, Inc, Irvine, CA, USA) were both freely offered at the Cardiac Surgery Department, Beijing Anzhen Hospital. The recurrence of AF postablation was defined as a recurrence of AF more than 3 months following AF ablation, within 3 months defined as early recurrence. Episodes of atrial tachycardia or atrial flutter were also classified as a recurrence.[17)]

Statistical analysis

All the statistical analyses were conducted using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). A two-sided P <0.05 was considered statistically significant. All continuous variables were expressed as the mean ± standard deviation (SD). Normality of distribution of all continuous variables was verified using the Kolmogorov–Smirnov tests. While considering the data among the ANP level, measurements of LAV, LAEF, LAPEF, and LAAEF as well as the peak velocity of the A wave were considered independent factors, and an analysis of repeated measurements of variance was used. If the Mauchly sphericity test was significant (P <0.05), we applied the Greenhouse–Geisser adjustment for degrees of freedom. Post hoc pairwise comparisons with Bonferroni adjustments were conducted, and the new critical P value calculated was 0.0024 (0.05/21).

Results

Follow-up results, mortality, and complications

The surgical procedure, including pulmonary vein isolation, LAA excision, and ligament of Marshall resection, was successfully completed in all patients. Five patients (9.6%) had AF recurrences, while one patient (1.9%) had new-onset paroxysmal left atrial flutter episodes following surgical ablation. A total of 46 patients (88.5%) were prospectively followed over 3 months in terms of their sinus rhythm postprocedure. There were no early deaths and no severe operative complications, including thromboembolic events, and none of the patients needed pacemaker implantation.

Left atrial dynamic function

During follow-up, atrial volume was detected using a transthoracic UCG with apical four-chamber views. There was a significant decrease in LAV_{max} 7 days postprocedure (65.39 ± 17.97 mL) compared with that preprocedure (69.30 ± 19.19 mL; P <0.001). This difference persisted when assessed 3 months postprocedure (64.65 ± 17.44 mL; P <0.001). Similar changes were noted in LAV_p (**Table 2**). However, there was no significant change 7 days postprocedure (44.67 ± 12.86 mL) compared with 3 months postprocedure (44.78 ± 12.00 mL; P = 0.807). Furthermore, there was also a significant decrease in LAV_{min} 3 months postprocedure (29.54 ± 9.01 mL) compared with the baseline preprocedure (31.46 ± 10.52 mL; P <0.001). However, LAV_{min} was significantly higher 7 days postprocedure (32.67 ± 10.10 mL) than that preprocedure (P = 0.002).

The left atrial hemodynamic changes are summarized in **Table 3**. LAEF was significantly lower 7 days postprocedure (50.09 ± 4.96%; P <0.001) than that preprocedure (54.98 ± 4.03%). However, these levels returned to the preprocedure levels when assessed 3 months postprocedure (54.41 ± 4.54%; P = 0.235). The peak velocity (cm/s) displayed similar changes (**Table 3**). LAPEF exhibited a persistent decrease when measured 7 days (31.72 ± 4.32%) and 3 months (30.41 ± 5.39%) postprocedure compared with baseline level (33.37 ± 4.16%; P <0.0024). However, there was a significant increase in LAAEF at 3 months postprocedure (34.46 ± 4.52%; P = 0.001), which decreased 7 days postprocedure (26.98 ± 4.42%; P <0.001) compared with that preprocedure.

Impact of LAA excision on ANP secretion

Blood samples for assaying ANP levels were drawn at three time points, as described in the Methods section. Seven days postprocedure (2.89 ± 0.83 pg/mL) and at 3 months (2.92 ± 0.67 pg/mL), the ANP levels were not significantly different compared with the pre-LAA excision baseline levels (3.02 ± 0.77pg/mL, F = 1.019, P = 0.350).

Discussion

A series of studies have demonstrated that prolonged AF results in the loss of effective atrial contraction and atrioventricular synchrony.[2,6,7,21–23)] In this prospective, self-controlled study, we evaluated left atrial volume and left atrial hemodynamic performance by real-time three-dimensional echocardiography. The LA size at baseline was obviously beyond the cutoff of 35 mm for the enrolled AF patients. Not surprisingly, there is general agreement that the deleterious effects of AF include the loss of atrial muscle mass and fibrotic changes within the

Table 2 Left atrial volume changes perioperatively

Volume (ml)	Preprocedure	7 days postprocedure	3 months postprocedure	*P*	F
LAV_{max}	69.30 ± 19.19	65.39 ± 17.97*	64.65 ± 17.44*	<0.001	83.744***
LAV_p	46.22 ± 13.40	44.67 ± 12.86*	44.78 ± 12.00*	0.001	7.548
LAV_{min}	31.46 ± 10.25	32.67 ± 10.10*	29.54 ± 9.01*,**	<0.001	34.111

*P values for comparison of statistical difference with preprocedure volume (P <0.0024); **P values for comparison of statistical difference with 7 days postprocedure (P <0.0024); ***Greenhouse–Geisser adjustment (P <0.05).LAV_{max}: left atrial maximum volume; LAV_p: left atrial preatrial contraction volume; LAV_{min}: left atrial minimal volume

Table 3 Left atrial hemodynamic changes perioperatively

Fraction (%)	Preprocedure	7 days postprocedure	3 months postprocedure	*P*	F
LAEF	54.98 ± 4.03	50.09 ± 4.96*	54.41 ± 4.54**	<0.001	55.853
LAPEF	33.37 ± 4.16	31.72 ± 4.32*	30.41 ± 5.39*	<0.001	12.306***
LAAEF	32.47 ± 3.50	26.98 ± 4.42*	34.46 ± 4.52*,**	<0.001	80.971
A peak velocity (cm/s)	62.26 ± 5.41	53.30 ± 6.80*	61.93 ± 5.60**	<0.001	144.955***

*P values for comparison of statistical difference with preprocedure volume (P<0.0024); **P values for comparison of statistical difference with 7 days postprocedure (P<0.0024); ***Greenhouse–Geisser adjustment (P<0.05). LAEF: left atrial ejection fraction; LAPEF: left atrial passive ejection fraction; LAAEF: left atrial active ejection fraction

atrial myocardium.[22] Furthermore, there was a 3%–6% decrease in LAV_{max}, $LAV_{min,}$ and LAV_p after the surgical ablation of AF. One explanation for these findings could be consistent with reverse modeling, and another possible reason for a decrease in left atrial volume is scar-related contracture from the surgical ablation injury site. Lakkireddy et al[11] showed that elimination of the LAA in patients with AF could result in downregulation of the RAAS, further leading to a reduction in LA volume.

In the present study, LAAEF significantly decreased 7 days postsurgery and increased at 3 months compared with that at baseline. LAPEF significantly decreased 7 days postsurgery and continued to decrease 3 months postsurgery. These findings suggest that surgical ablation in patients with paroxysmal AF who are predominantly in sinus rhythm improves contractile left atrial function (or LAAEF) in patients without structural heart disease. Our findings are in accordance with the previous report of La Meir et al,[24] who demonstrated improved atrial function and reverse remodeling after successful minimally invasive radiofrequency ablation. This phenomenon might be explained by atrial stunning, which may last for several weeks and result in a reduction in the mechanical function of the left atrium in AF after the restoration of sinus rhythm. Thomas et al.[25] have shown a gradual recovery of left atrial contractile function following cardioversion. However, our study also showed that LA conduit function (or LAPEF) was impaired significantly according to follow-up echocardiography. Several studies have reported that LAA contractile function contributes greatly to LA transport function. Benussi et al.[26] studied the effects of LAA amputation on left atrial function in the setting of minimally invasive surgical pulmonary vein isolation and found that the LA reservoir and conduit function are impaired after procedure. This might contribute to the decreased LA compliance resulting from the postoperative adhesions of the pericardium and/or atrial surgical scarring. Furthermore, LA conduit function was greatly influenced by the left ventricle diastolic component. More research on this topic with longer follow-up periods is warranted.

Moreover, several studies have shown that the LAA is largely involved in ANP secretion and plays an important role in body fluid modulation.[7,11] In a clinical study, Yoshihara et al.[27] demonstrated that ANP secretion was attenuated in the early postoperative period after the Maze procedure, including bilateral atrial appendectomy, and it persisted in the chronic phrase. Concurrently, this attenuated ANP directly affects body fluid balance during the early postoperative period. Omari et al.[28] previously reported that plasma ANP levels were reduced after right atrial appendectomy in patients who underwent an elective coronary artery bypass operation. Wang et al.[29] also demonstrated that plasma ANP levels were significantly lower after right atrial appendectomy in Chinese patients who underwent concomitant prosthetic mitral valve replacement and the Maze procedure. In the present study, there was no significant difference in ANP levels preprocedure, although the levels decreased slightly 7 days after surgery and recovered gradually 3 months after surgery. This difference might be attributable to ANP secretion sites, for example, ANP levels in the right atrial appendages were 40-fold higher than those in the remainder of the atrial free wall and the ventricles. Recently, Lakkireddy et al.[11)] also performed a clinical analysis to compare the effects of epicardial or endocardial LAA devices on the neurohormonal profiles of patients. They quantitatively examined the levels of key hormones in the adrenergic, renin–angiotensin–aldosterone, metabolic system as well as natriuresis immediately before the procedure and immediately after device deployment as well as 24 h and 3 months postprocedure. In the cited study, the ANP concentration finally returned to the pre-epicardial or endocardial LAA device baseline level when assessed 3 months postprocedure, a finding that corresponds well with that of our present study. Although successful surgical excision was defined as residual pouch remaining in the LAA <1 cm, theoretically, recovery of ANP may be simply a function of the residual tissue increasing activity.

Study limitations

Our study had some important limitations. First, it is insufficient to obtain an adequate statistical power based on a relatively small sample size. Further follow-up studies with large sample sizes and multiple comparisons are warranted to determine the long-term effects of minimally invasive surgery on LA function based on the current observations. Second, there were no controls enrolled in this pilot study. This study was not powered to evaluate stroke prevention. Third, we did not measure other neurohormonal factors except for ANP, for example, the adrenergic system, RAAS system, lipids and glucose metabolism, which have been reported to change during the operation. Finally, we included in the study only paroxysmal AF patients who might present with minor changes in LA tissue and muscle. Because of limited information on this topic, further studies in carefully selected study participants and animal models are also needed to elucidate the underlying physiological changes.

Conclusion

There are no significant differences in left atrial dynamics or natriuretic peptide levels in patients undergoing minimally invasive surgery with LAA excision for AF. Our findings need to be further confirmed by prospective randomized studies involving reasonably sized populations.

Disclosure Statement

The authors declare that there is no conflict of interest.

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