Effect of Left Atrial Activity After the Maze Procedure on Clinical and Echocardiographic Outcomes

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Background: Although the maze procedure reduces the risk of adverse cardiac events, the clinical importance of post-maze left atrial (LA) activity on long-term surgical outcomes is not well defined.

Methods and Results: Between January 2000 and December 2009, 416 consecutive patients with sinus conversion after a modified Cox III procedure with cryoablation were enrolled and subdivided into patients with restored LA activity (group ReA; n=231) and those without LA activity (group NoA; n=185) assessed using Doppler echocardiographic examination at 3–6 months after the maze procedure. During the long-term follow-up (4.6±2.6 years), the NoA group showed more frequent major adverse events (P=0.001) including cardiac death (P=0.145), heart failure events (P=0.032), and thromboembolic stroke (P=0.048) than the ReA group. In multivariate analysis, lack of LA activity was associated with a 2.2-fold increased risk for major adverse events (95% confidence interval [CI], 1.1–6.8; P=0.029) and with a 2.4-fold increased risk for late progression of tricuspid regurgitation (95% CI, 1.0–3.5; P=0.041).

Conclusions: Absence of LA activity after the maze procedure was independently associated with a significantly increased risk of major adverse events and late progression of tricuspid regurgitation. (Circ J 2014; 78: 1584–1592)

Key Words: Atrial fibrillation; Atrial mechanical function; Heart valves; Maze procedure

The maze procedure is a useful modality for sinus rhythm (SR) restoration in patients with atrial fibrillation (AF) undergoing cardiac valve surgery. The contemporary modified Cox maze III procedure has an excellent success rate for SR recovery up to 90%. However, several studies have shown that the left atrium may fail to regain full activity even in the presence of restored SR after the maze operation. Although the maze procedure has been shown to reduce thromboembolic complications and to improve hemodynamic performance, it is not known whether these advantages also exist in patients without atrial activity. Our aim in this study was to evaluate the effect of post-maze left atrial (LA) activity on long-term clinical and echocardiographic outcomes in patients who underwent the procedure.

Methods

Patient Population
Between January 2000 and December 2009, 508 consecutive patients underwent a modified Cox maze III procedure using cryoablation with other cardiac operations. We preferentially enrolled patients who showed successful rhythm control with the cryo-maze procedure, defined as those who recovered SR within the period of 3–6 months after the maze operation and thereafter showed no evidence of AF recurrence irrespective of antiarrhythmic drug use during the follow-up period. Of the 508 patients, 416 who satisfied the definition of successful rhythm control were finally enrolled. Patients were divided into 2 groups: those in whom LA activity was restored (ReA group; n=231) and those without LA activity (NoA group; n=185) at the end of the defined postoperative period. The institutional review board approved the study protocol and waived the need for informed consent from patients or relatives.

Operative Technique
The principles and detailed surgical procedures of the modified Cox maze III procedure using cryoablation have been previously described and were maintained throughout this study. Cryogenerators were set at –60°C and each cryoablation was performed for 120–150 s to create transmural lesions. LA box and connecting lesions into the posterior mitral annulus were made. The reduction of the LA dimensions by partial resection

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of the atrial wall was performed. The LA appendage was obliterated internally using a running suture with 4-0 prolene. Other techniques such as external ligation, external stapled excision, stapled excision, or a combination of techniques were not performed. A right atrial (RA) isthmus lesion was created and extended to the LA incision. We occasionally added a lesion from the RA appendage to the tricuspid valve annulus in cases of a dilated RA. Modified ultrafiltration was used routinely.

Postoperatively, oral amiodarone 200 mg/day was administered for 2–3 months and then withdrawn if there was no AF recurrence. If patients showed AF during their hospital stay, 20–40 mg/h of amiodarone was given intravenously and followed by oral amiodarone of 200 mg twice daily and then 200 mg/day. Electrical cardioversion was used only in patients with atrial flutter-fibrillation. After 3–6 months, oral anticoagulation was withdrawn in the absence of thrombogenic risks such as prior stroke history and mechanical valve replacement. Standard 12-lead ECG was assessed at 1, 3, 6, 9, and 12 months postoperatively and every 6 months thereafter.

Follow-up and Study Endpoints
Most of the patients (88.2%, 367/416) were followed-up every 3 months at Samsung Medical Center and the mean follow-up duration was 4.6±2.6 (maximum, 10.2) years. For 48 patients (11.5%), survival status and follow-up data were obtained by telephone and outpatient interviews at other institutions. Survival data for 1 patient were obtained from the national death registry and survival database (1/416, 0.2%).

The primary endpoint of the study was major adverse cardiac/cerebrovascular events (MACE), including cardiac death, heart failure (HF) events, and thromboembolic stroke. Cause of death was classified as cardiac (sudden death or HF) or noncardiac. HF events included readmission for aggravated HF symptoms or an unplanned visit to emergency room with changes in medications such as diuretics, vasodilators, or inotropic agents. Postoperative stroke was defined as the development of a new focal neurologic deficit confirmed by neurologists after imaging studies using computed tomographic or magnetic resonance imaging.

Cardiac reoperation, infective endocarditis, and progression of tricuspid regurgitation (TR) were also evaluated. Transthoracic echocardiography was performed prior to surgery, before discharge, and during follow-up (3–6 months and then 1, 3, 5, >7 years after surgery). Left ventricular (LV) end-systolic and diastolic dimensions were obtained from the parasternal view based on the American Society of Echocardiography guidelines. The LV ejection fraction (EF) was calculated using Simpson’s method from the parasternal view. LA volumes were assessed by using the ellipsoid (length-diameter) method and corrected to body surface area (LA volume index, LAVI). Transmitral peak velocities of the early (E) and late (A) filling waves were measured in the apical 4-chamber view (Figure 1). Peak A-wave velocity <10 cm/s was considered to indicate absence of atrial mechanical contraction.

There was 98% and 95% intra- and interobserver agreement, respectively, for the recovery of LA activity when reviewed by 2 independent examiners who were blinded to each other’s judgment. Early diastolic peak velocity of the septal mitral annulus (E’v) was measured with tissue Doppler imaging. All 416 patients were in SR during the echocardiographic examinations. According to previous studies, the degree of TR was assessed using the vena contracta width and the ratio of the maximal jet area to the corresponding RA area averaged in the parasternal and apical views; vena contracta width ≥7 mm defines severe TR and jet area/RA area ratio <20%, 20–34%, and >34% indicate mild, moderate, and severe TR, respectively. For statistical analysis, TR was graded from 0 to 4. The right ventricular systolic pressure (RVSP) was estimated according to the standard guidelines for the right heart in adults; RVSP was calculated using the simplified Bernoulli equation from the peak TR jet velocity and the estimated value of the RV pressure. RA pressure was estimated from the inferior vena cava with respiratory variation.

The mean duration of echocardiographic follow-up was 3.3±2.5 (maximum, 9.8) years.

Statistical Analysis
Statistical analyses were performed using PASW Statistics 21 software (SPSS Inc, Chicago, IL, USA). For comparisons between 2 groups, the χ² test or Fisher’s exact test was used for categorical variables, and the unpaired Student’s t test was used for continuous variables. Repeated measure ANOVA was used to compare echocardiographic parameters at different...
Results

Patients’ Characteristics and Operative Data

Baseline characteristics of the patients are listed in Table 1. Of 231 patients in the ReA group, 119 (51.5%) showed LA activity at discharge and 112 (48.5%) recovered LA activity within 6 months after the surgery. However, there were no changes in the status of LA activity after this period in any patient. The NoA group had a longer AF duration, a higher incidence of HF history, a lower LVEF, a greater LAVI, a higher RVSP, a higher E-wave velocity, and a greater E/E’ ratio than the ReA group. However, there was no significant difference between
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The 2 groups in terms of age, sex, body surface area, AF type, or presence of hypertension, rheumatic heart disease, stroke history, chronic kidney disease, or LV dimensions.

Operative data are listed in Table 2. More mitral valve replacements and tricuspid valve repairs were performed in the NoA group than in the ReA group. The number of cases of coronary artery bypass graft surgery was similar in the 2 groups.

Clinical and Echocardiographic Outcomes

Clinical outcomes are summarized in Table 3. The overall mortality and total stroke rates were 4.3% (18/416) and 3.8% (16/416), respectively, and HF events occurred in 15 patients (3.6%) during the follow-up. The NoA group showed a higher incidence of HF events (P=0.032) and thromboembolic stroke (P=0.048) than the ReA group. Although statistically insignificant, there was a tendency toward more cardiac deaths in the NoA group than in the ReA group (P=0.145). Therefore, the rate of MACE including cardiac death, HF events, and thromboembolic stroke was significantly higher in the NoA group vs. the ReA group (P=0.001, Figure 2). Additionally, more cardiac reoperations were performed in the NoA group than in the ReA group; the causes of cardiac reoperation in the NoA group were infective endocarditis (n=3), failure of valve repair (n=2), and severe TR (n=1). The cause of reoperation in the ReA group was constrictive pericarditis.

The effect of LA activity on several echocardiographic parameters was also evaluated. All comparisons were performed after adjusting for differences in baseline echocardiographic parameters. No significant differences were observed between the 2 groups in terms of age, sex, body surface area, AF type, or presence of hypertension, rheumatic heart disease, stroke history, chronic kidney disease, or LV dimensions.

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associated with HF events, thromboembolic stroke, MACE, and TR progression (Table 4). However, in the multivariate analysis, absence of LA activity was identified as an independent predictor of HF events, MACE, and TR progression even group than in the RA group at late follow-up (Figure 4).

**Effect of LA Activity on Long-Term Outcomes**

Univariate analysis revealed that absence of LA activity was associated with HF events, thromboembolic stroke, MACE, and TR progression (Table 4). However, in the multivariate analysis, absence of LA activity was identified as an independent predictor of HF events, MACE, and TR progression even
after adjustment for relevant variables shown in Table 4. In addition to LA activity, hypertension was independently associated with cardiac mortality, HF events, thromboembolic stroke, and MACE.

**Discussion**

**Main Findings**

We investigated the effect of LA activity on clinical and echocardiographic outcomes in patients who underwent a successful modified Cox maze III procedure using cryoablation. The main findings are: (1) LA mechanical activity was not observed in 44% of patients during follow-up; (2) lack of LA activity was independently associated with HF events and MACE, although it was associated with thromboembolic stroke events only in the univariate analysis; (3) absence of LA activity correlated with increased LAVI, elevated RVSP, and a 2.4-fold increase in the risk for late progression TR to a moderate or greater degree.

**Beneficial Effect of LA Activity on Long-Term Outcomes**

The maze procedure has been reported as effective at restoring SR in patients with AF. However, the rate of recovery of LA activity has been quite variable, from 21% to 95%, being at least partly affected by the etiology of AF. Kobayashi et al showed that 90% of patients with an atrial septal defect had restored atrial contraction after the maze procedure, whereas in patients with mitral valve disease, the recovery rate ranged from 21% to 90%. In our study population, in which 62% of patients had rheumatic heart disease, the recovery rate of LA activity was 54%, which is consistent with the findings form Feinberg et al’s study in which only 60% of patients showed evidence of LA contraction after a mean follow-up period of 8 months after the maze procedure. The recovery of LA activity after the maze procedure can augment LV filling and stroke volume. Therefore, the lack of LA activity could predispose patients to the development of HF by decreasing forward cardiac output and elevating LA pressure. Indeed, in our data the E/E’ ratio, which reflects LA pressure, was significantly higher in the NoA group compared with the ReA group (P=0.028). Additionally, HF-related readmission or unplanned visit to the emergency room was more frequently observed in the NoA group than in the ReA group (P=0.032). A higher LA pressure in the NoA group could induce a greater increase in LAVI directly and in RVSP backwardly with indirectly.

Kawaguchi et al showed that the LA dimensions decreased significantly after the maze procedure in patients with AF and valve disease. In contrast, without the maze procedure, the LA dimensions decreased transiently early after valve surgery, but subsequently returned to preoperative levels. This preventive effect of the maze procedure against LA positive remodeling might be related to the maintenance of LA mechanical activity. The recovery of LA activity may also contribute to the prevention of AF-related stroke or thromboembolism by increasing the blood flow velocity in the LA. According to a recent study by Buber et al, 47 (31%) of 150 patients with recovered SR after the maze operation showed no evidence of LA mechanical contraction at 3-month follow-up echocardiography and the absence of LA contraction resulted in a significant increase in the risk for thromboembolic stroke in patients with SR. In our data incorporating only cryo-maze cases to ensure homogeneity of the study population, lack of LA activity was associated with thromboembolic stroke events only in the univariate analysis; (3) absence of LA activity correlated with increased LAVI, elevated RVSP, and a 2.4-fold increase in the risk for late progression TR to a moderate or greater degree.

Approximately half of the patients (49.3%, 205/416) in our series, proportion that is twice as high as in Buber et al’s study, underwent mechanical valve replacement; therefore, the protective effect of LA activity against subsequent thromboembolic complications might have been diluted by long-term anticoagulation therapy. Additionally, the obliteration of the LA appendage in all of the present study’s patients might also attenuate further the beneficial effect of LA activity against thromboembolic complications. Therefore, even in the subgroup without mechanical valves (n=211), the incidence of thromboembolic stroke was not significantly different depending on the presence of LA contraction (ReA vs. NoA group,
Kim et al. found that AF predisposed patients undergoing mitral valve surgery to late TR progression, which could be prevented by the maze operation. In addition, they showed that the absence of RA mechanical activity was a predictor for progression of late TR in a subgroup analysis of 38 patients who had 1/128 vs. 2/83; P=0.563).

Another interesting observation was that absence of LA activity was a significant predictor of late progression of functional TR after cardiac surgery. Late TR is known to adversely affect cardiac mortality and morbidity. AF, LA enlargement, and RV dysfunction have been identified as important factors in late TR after left-side cardiac surgery. Kim et al. found that AF predisposed patients undergoing mitral valve surgery to late TR progression, which could be prevented by the maze operation. In addition, they showed that the absence of RA mechanical activity was a predictor for progression of late TR in a subgroup analysis of 38 patients who had
undergone the maze operation. In our series, LA activity was a strong protective factor against late TR progression. Few studies have demonstrated a causal relationship between LA activity and late TR progression and our findings may shed light on the causes of late TR after cardiac surgery.

Taking all these effects together, lack of LA activity was associated with a 2.2-fold increase in the risk of MACE and a 2.4-fold increased risk for late progression of TR severity during long-term follow-up after the maze procedure in our series. Moreover, when the 416 patients were divided into 3 groups according to the degree of A-wave amplitude, there was a clear trend toward a higher rate of adverse outcomes as the degree of A-wave amplitude decreased (Figure S1). However, we acknowledge that additional studies are needed to confirm the favorable effects of LA activity. On the other hand, our data showed that the NoA group had a longer AF duration and more severe dilatation of their baseline LA (Table 1), so further investigations might be worthwhile to determine whether earlier maze and valve surgery would lead to a higher recovery rate of LA activity and better long-term clinical outcomes in patients with gray zone indications for valve surgery.

On the other hand, several parameters such as AF duration, preoperative LV EF, LAVI, and RVSP seemed not closely associated with long-term outcomes in our results, although these parameters are generally considered to affect long-term outcomes. This result might be at least partly related to quite low numbers of long-term events: cardiac death (2.9%), HF (3.6%), and thromboembolic stroke (1.7%). Therefore, our study population might not be large enough to show a statistical difference. In addition, lack of A-wave might be caused not only absence of LA activity but also by a very stiff LV. The NoA group showed worse diastolic dysfunction; the E/E' ratio was significantly higher in the NoA group and there was a trend toward a lower E'-wave in the NoA group compared with the ReA group. Therefore, not only inactive atrial mechanical function but also worse diastolic function might contribute to a worse prognosis in the NoA group. Therefore, our data must be interpreted with caution.

Study Limitations
Several limitations of the present study require consideration. The study was inherently limited by its retrospective nature, although it is difficult to plan prospective studies of such long duration. However, our cohort is one of the largest, with most of the patients treated with the same manner (cryo-maze) and by the same surgeon. Data collection errors were minimized because our echocardiographic procedure was standardized and the results were recorded in an electronic database. Second, the groups were not randomized into anticoagulation therapy, so we could not evaluate whether a possible relationship existed between stroke events and the adequacy of anticoagulation. Third, more detailed quantifications of stroke volume, cardiac output, and TR grade were not performed. Finally, we acknowledge that the ellipsoid method used to measure LA volume in our study could underestimate it and that the biplane method of disks or the biplane area-length method is more accurate.

Conclusions
Despite the recovery of SR after the maze operation, atrial mechanical function could remain impaired. Restoration of LA activity was beneficial to long-term composite clinical outcome including cardiac death, HF events, and thromboembolic stroke. Furthermore, recovery of LA activity showed an additional protective effect against late progression of TR after the maze surgery.

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Disclosures
None.

References
13. 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: 1440–1463.

**Supplementary Files**

**Supplementary File 1**

**Figure S1.** Clinical outcomes depending on the degree of recovered A-wave amplitude.

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-13-1390