Sick Sinus Syndrome After the Maze Procedure Performed Concomitantly With Mitral Valve Surgery

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Background—To characterize the development of sick sinus syndrome (SSS) after the additive maze procedure (MP) during mitral valve surgery.

Methods and Results—Follow-up data (median, 3.6 years) of 750 patients with a prevalence of rheumatic cause of 57.6% were analyzed. SSS occurred in 35 patients with a time-dependent increase: the incidence rates at 1, 2, and 4 years after surgery were 2.9%, 3.7%, and 4.3%, respectively. The additive MP showed higher risks of SSS development (hazard ratio, 7.44; 95% confidence interval, 3.45–16.05; \( P<0.001 \)) and pacemaker implantation (hazard ratio, 3.61; 95% confidence interval, 1.95–6.67; \( P<0.001 \)). Patients who developed SSS showed higher 4-year rates of clinical events (death, stroke, and hospital admission) (67.5±8.5% versus 33.0±1.9%; \( P<0.001 \)). After adjustment for age and preoperative peak systolic pulmonary artery pressure, the lesion extent (biatrial versus left atrial MP), not the underlying cause (rheumatic versus nonrheumatic), was independently associated with SSS development (hazard ratio, 3.58; 95% confidence interval, 1.08–11.86; \( P=0.037 \)). The adverse effect of the biatrial MP was confirmed in patients with trivial or mild preoperative tricuspid regurgitation showing higher SSS incidence (4.6±1.4% versus 1.0±0.7%; \( P=0.023 \)), not in those with moderate-to-severe tricuspid regurgitation (6.8±1.7% versus 3.8±3.8%; \( P=0.337 \)). Recurrence of atrial fibrillation was not associated with the lesion extent of the MP.

Conclusions—After the additive MP, the ongoing risk of SSS development should be acknowledged irrespective of the underlying cause. Considering additive risk of biatrial MP with similar atrial fibrillation recurrence rate, minimizing lesion extent is warranted. (J Am Heart Assoc. 2018;7:e009629. DOI: 10.1161/JAHA.118.009629.)

Key Words: atrial fibrillation • maze procedure • mitral valve surgery • sick sinus syndrome

The Cox-maze procedure (MP) is a well-established method of rhythm control in patients with atrial fibrillation (AF).\(^1,2\) In previous randomized trials or observational registries, this procedure has been demonstrated to have excellent efficacy in terms of rhythm control and adverse outcomes after mitral valve (MV) surgery (MVS).\(^3−7\) The development of symptomatic bradyarrhythmia is a well-known major complication of the MP, which can be fatal or necessitate pacemaker implantation. Previous studies have reported a wide incidence of 2% to 21% during short-term follow-up after surgery; and age, extended lesion set, and microwave energy source were identified as predictors of sinus node dysfunction or sick sinus syndrome (SSS).\(^4,8−10\) However, these observations are not sufficient to change practice patterns and several issues remain unresolved. Although rheumatic pathological characteristics reportedly show a high prevalence of anti–sinus node antibodies that may contribute to SSS development after cardiac surgery,\(^11\) the underlying cause of the MV disease has not been adequately addressed. Moreover, most of the existing clinical studies had a relatively short clinical follow-up duration of 1 year.\(^4,10,12\) Thus, it remains unknown whether there is a cumulative or time-dependent risk of SSS development after the MP, and the impact of age or lesion extent (biatrial versus

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Clinical Perspective

What Is New?

- The additive maze procedure during mitral valve surgery showed higher risks of development of sick sinus syndrome and pacemaker implantation.
- The biatrial versus left atrial maze procedure, not the underlying cause of mitral valve disease, was associated with sick sinus syndrome development, without any additive benefit of rhythm control.
- The adverse effect of the biatrial maze procedure was statistically significant in the subgroup of patients with trivial or mild preoperative tricuspid regurgitation.

What Are the Clinical Implications?

- Tailored selection of lesion extent (biatrial versus left atrial) appears appropriate for the additive maze procedure during mitral valve surgery.

left atrial [LA] maze) has not been completely evaluated. These data are clinically important for defining the group of patients who would benefit the most from MPs. Therefore, in the current study, we sought to evaluate the pattern of SSS development by using clinical data with a relatively long follow-up duration and to determine whether the underlying cause of the MV disease and the lesion extent of the MP could affect SSS development.

Methods

We will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author on reasonable request.

Data Collection and Analysis

The patients' baseline characteristics and electrocardiographic, echocardiographic, surgical, and outcome data were obtained by carefully reviewing their medical records in standardized case report forms. Data on baseline demographic characteristics and comorbidity status were gathered during admission for MVS. The patients usually attended follow-up visits at 1, 3, and 6 months after MVS and every 6 months thereafter. Holter monitoring was usually prescribed during admission and at the first outpatient visit. Twelve-lead electrocardiographic data were recorded at every outpatient visit. Follow-up data were collected via a direct telephone interview and through a detailed review of all medical records. The cause and date of death in mortality cases were confirmed using information in death certificates, along with a review of all available clinical records at the time of death. The median follow-up duration was 3.6 (interquartile range, 1.7–6.4) years. The cause of the MV disease was evaluated by 2 cardiologists (J.-K.S. and M.S.C.) by using the echocardiographic images, and the intraobserver and interobserver variabilities in rheumatic cause were found to be excellent, with $\kappa$ values of 0.96 and 0.91, respectively. Discordant cases were resolved using surgical findings.

Surgical Procedure

All patients underwent MV replacement or repair concomitantly with the MP at the discretion of cardiac surgeons together with the recommendations of cardiologists. The decision on performing a tricuspid valve (TV) surgical intervention was made by the in-house cardiosurgical team, on the basis of the preoperative echocardiographic findings as well as on-site findings in the operation room. The extent and details of the MP were determined by the cardiac surgeons, and a detailed description of the surgical procedure has previously been reported by the surgical members of our team.\(^5\)\(^,\)\(^13\) In brief, after aorta clamping and LA incision, LA ablation was performed endocardially before the MV procedure. LA ablation lesions included a single-box lesion for pulmonary vein isolation, a line from the box lesion to the left appendage, and a mitral isthmus line connecting the box lesion and the MV annulus. Additional epicardial coronary sinus ablation was performed on the opposite side of the mitral isthmus lesion. The right atrial (RA) lesion set consisted of a cavotricuspid isthmus line and a line from the isthmus lesion to the superior vena cava. This simplified modification of the Cox-MP was intended to minimize the area of isolation and avoid damage to the normal conduction system. The decision to perform the RA ablation was made on the surgeon’s discretion, influenced by an individual patient’s risk of recurrent AF, such as age, atrial size, AF wave pattern on
ECG (fine or coarse), or necessity of surgical procedure for tricuspid regurgitation (TR).

**Study Outcomes and Definitions**

The primary outcome of the current study was SSS development, defined as symptomatic sinus bradycardia associated with documented sinus exit block, pause, or arrest in any type of electrocardiographic data, including 12-lead ECG, Holter monitoring, or telemetry record. Transient asymptomatic postoperative junctional rhythm, which disappeared during the convalescence period or by the first outpatient clinic visit, was not counted as a clinical event. The rate of high-degree atrioventricular block (AVB), including documented Mobitz type II or complete AVB, and PPM implantation were defined as secondary outcomes. For the evaluation of the efficacy of the MP, recurrent AF lasting ≥30 seconds in Holter monitoring or sufficiently long for a 12-lead ECG to be recorded after 90 days of blanking period from index surgery was also defined as a secondary outcome of the current study. The rates of clinical outcomes, including death, stroke, and unexpected rehospitalization after surgery, were compared between patients with and those without SSS development throughout the follow-up period after the index surgery.

**Statistical Analysis**

Summary statistics are presented as frequencies and percentages or as means±SD. Differences between 2 groups were compared using unpaired Student t test or Mann-Whitney U test for continuous variables and χ² test or Fisher’s exact test for categorical variables. To identify the factors associated with SSS development, univariate and multivariate Cox proportional hazard models were used. The proportional hazard assumption was tested by examining the log(-log[survival]) plot and partial Schoenfeld residuals. In multivariate analysis, backward elimination techniques were used to define the independent predictors of SSS development. Cumulative survival rate and event-free survival rate curves were generated using the Kaplan-Meier method and compared using the log-rank test. To compensate for the nonrandomized design of the current study and reduce the number of potential confounding factors, we used propensity scoring in the subgroup analysis in patients without moderate to severe TR. A logistic regression model was used to compute propensity scores. Covariates included age, sex, body mass index, hypertension, diabetes mellitus, congestive heart failure, cerebrovascular accident, coronary artery disease, prior cardiac surgery, rheumatic pathological features, LA and RA areas, left ventricular ejection fraction, TR pressure.
gradient, moderate-to-severe mitral stenosis, and moderate-to-severe mitral regurgitation. Model discrimination was assessed using C-statistics, and model calibration was assessed using Hosmer-Lemeshow statistics. Weighted Cox’s proportional hazards models were fitted using the inverse probability of treatment weighting method, and relative outcomes were analyzed accordingly. All P values were 2 sided, and P<0.05 was considered statistically significant. All statistical analyses were performed using R software version 3.2.2 (http://cran.r-project.org/).

Results
Between 2006 and 2014, 750 patients (age, 56.8±12.2 years) underwent MVS and the MP at our institution. The 2 most common causes of MV disease included rheumatic disease (n=431, 57.6%) and MV prolapse or chordae rupture (n=249, 33.2%). Moderate-to-severe mitral regurgitation was the most common valvular dysfunction and was observed in 523 patients (69.7%). MV replacement was performed in 446 patients (59.5%), and MV repair was performed in 304 patients (40.5%). The biatrial MP was performed in 513 patients (68.4%), and the LA MP was performed in 237 patients (31.6%) (Figure 1). Concomitant TV surgery was performed in 402 patients (53.6%), most of whom underwent TV repair (n=385, 95.8%).

SSS After the MP
During the follow-up period, SSS and AVB occurred in 35 (4.7%) and 7 (0.9%) patients, respectively, and PPM was implanted in 28 patients (80.0%) with SSS and in 6 patients (83.3%) with AVB. Compared with patients who underwent MVS only, those who underwent concomitant MVS and the MP showed higher risks of SSS development (hazard ratio [HR], 7.44; 95% confidence interval [CI], 3.61–12.46; P<0.001) and PPM implantation (HR, 3.61; 95% CI, 1.95–6.67; P<0.001). However, the risk of AVB development was not significant (HR, 1.49; 95% CI, 0.58–3.86; P=0.411) (Figure 2). The temporal pattern of symptomatic bradyarrhythmia development is also shown in Figure 2. AVB development was mostly confined to the immediate postoperative period, whereas SSS showed a gradual increase during follow-up after the surgery, with incidence rates at 1, 2, and 4 years after surgery of 2.9%, 3.7%, and 4.3%, respectively. In accordance with this pattern, the rate of PPM implantation also continuously increased during follow-up.

Patients who developed SSS showed a higher incidence of adverse clinical events (67.5±8.5% versus 33.0±1.9%; P<0.001) (Figure 3) driven by the higher incidence of rehospitalization (63.7±9.1% versus 23.5±1.8%; P<0.001) and stroke (15.1±6.2% versus 5.0±0.9%; P=0.026) than those who did not develop SSS. The mortality rate did not differ between patients who developed SSS and those who did not.

The baseline characteristics of patients with and without SSS are shown in Table 1. Patients with SSS were significantly older than those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR. However, the dominant type of valvular dysfunction, underlying cause of MV disease, biventricular systolic function, and LA diameter or area did not significantly differ between the 2 groups. The biatrial MP was more frequently performed in patients with SSS than in those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR. However, the dominant type of valvular dysfunction, underlying cause of MV disease, biventricular systolic function, and LA diameter or area did not significantly differ between the 2 groups. The biatrial MP was more frequently performed in patients with SSS than in those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR. However, the dominant type of valvular dysfunction, underlying cause of MV disease, biventricular systolic function, and LA diameter or area did not significantly differ between the 2 groups. The biatrial MP was more frequently performed in patients with SSS than in those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR. However, the dominant type of valvular dysfunction, underlying cause of MV disease, biventricular systolic function, and LA diameter or area did not significantly differ between the 2 groups. The biatrial MP was more frequently performed in patients with SSS than in those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR. However, the dominant type of valvular dysfunction, underlying cause of MV disease, biventricular systolic function, and LA diameter or area did not significantly differ between the 2 groups. The biatrial MP was more frequently performed in patients with SSS than in those without SSS (64.0±9.0 versus 56.5±12.2 years; P<0.001), with a larger RA area, higher maximal TR pressure gradient, and higher incidence of moderate-to-severe TR.
LA volume reduction procedure, did not differ significantly between the 2 groups. The prescription rate of amiodarone in the discharge medication was not significantly different between those with or without AF, and the use rate of other types of antiarrhythmic drugs was almost negligible.

In the univariate Cox-proportional hazards model, age, moderate-to-severe TR, maximal TR pressure gradient, biatrial MP, and RA area were associated with SSS development (Table 2). After the backward elimination procedure, age (per 10 years: HR, 1.75; 95% CI, 1.26–2.43; \(P<0.001\)), maximal TR pressure gradient (per 10 mm Hg: HR, 1.24; 95% CI, 1.02–1.50; \(P=0.032\)), and biatrial MP (compared with left-sided MP: HR, 3.58; 95% CI, 1.08–11.86; \(P=0.037\)) were found to be independent predictors of SSS development.

**Impact of Underlying Cause**

To evaluate the impact of the underlying cause of MV disease, clinical data of patients with rheumatic disease (n=431) were compared with those of patients with nonrheumatic disease (n=319). Patients with rheumatic valvular heart disease were characterized by younger age, female predominance, lower prevalence of hypertension or congestive heart failure, larger atrial size, and a higher prevalence of moderate-to-severe TR than those without (Table 3). Mitral stenosis was a more common type of dominant valvular dysfunction in patients with rheumatic pathological characteristics, whereas mitral regurgitation was dominant in patients with nonrheumatic pathological characteristics. The underlying cause of MV disease demonstrated no difference in the rate of SSS development, pacemaker implantation, AF recurrence, and composite clinical events after the MP (Figure 4).

**Impact of Lesion Extent**

A subgroup analysis was performed to evaluate the relationship between the lesion extent of the MP and TR severity. Among patients without moderate-to-severe TR, 266 (56.3%)
### Table 1. Baseline Characteristics of the Study Patients

| Characteristic                              | Total (N=750) | Patients With SSS (n=35) | Patients Without SSS (n=715) | P Value |
|---------------------------------------------|---------------|--------------------------|-----------------------------|---------|
| Age, y                                      | 56.8±12.2     | 64.0±9.4                 | 56.5±12.2                   | <0.001  |
| Men, n (%)                                  | 316 (42.1)    | 13 (37.1)                | 303 (42.4)                  | 0.662   |
| Body mass index, kg/m²                      | 23.9±3.3      | 23.8±3.2                 | 23.9±3.3                   | 0.793   |
| Hypertension, n (%)                         | 194 (25.9)    | 12 (34.3)                | 182 (25.5)                 | 0.333   |
| Diabetes mellitus, n (%)                    | 69 (9.2)      | 6 (17.1)                 | 63 (8.8)                   | 0.172   |
| Congestive heart failure, n (%)             | 67 (8.9)      | 2 (5.7)                  | 65 (9.1)                   | 0.704   |
| Chronic renal disease, n (%)                | 10 (1.3)      | 1 (2.9)                  | 9 (1.3)                    | 0.960   |
| Previous CVA, n (%)                         | 34 (4.5)      | 2 (5.7)                  | 32 (4.5)                   | >0.99   |
| Previous CAD, n (%)                         | 45 (6.0)      | 2 (5.7)                  | 43 (6.0)                   | >0.99   |
| Previous OHS, n (%)                         | 38 (5.1)      | 4 (11.4)                 | 34 (4.8)                   | 0.173   |

#### Echocardiography

| Characteristic                              | Total (N=750) | Patients With SSS (n=35) | Patients Without SSS (n=715) | P Value |
|---------------------------------------------|---------------|--------------------------|-----------------------------|---------|
| LV end-diastolic dimension, mm              | 54.6±9.1      | 53.9±9.9                 | 54.6±9.0                    | 0.636   |
| LA size, mm                                 | 57.5±9.5      | 59.2±13.1                | 57.4±9.3                    | 0.425   |
| LA area, mm²                                | 45.5±15.3     | 44.3±18.0                | 45.6±15.2                   | 0.617   |
| RA area, mm²                                | 25.8±10.6     | 29.7±12.0                | 25.6±10.5                   | 0.026   |
| LV ejection fraction, %                     | 56.3±8.6      | 58.4±7.0                 | 56.2±8.6                    | 0.138   |
| Moderate-to-severe MS, n (%)                | 307 (40.9)    | 14 (40.0)                | 293 (41.0)                  | >0.99   |
| Moderate-to-severe MR, n (%)                | 523 (69.7)    | 26 (74.3)                | 497 (69.5)                  | 0.680   |
| Rheumatic heart disease, n (%)              | 431 (57.6)    | 19 (54.3)                | 412 (57.6)                  | 0.830   |
| Moderate-to-severe TR, n (%)                | 278 (37.1)    | 21 (60.0)                | 257 (35.9)                  | 0.007   |
| TR PG, mm Hg                                | 38.3±14.8     | 45.5±15.3                | 38.0±14.7                   | 0.003   |

#### MV surgery

| Characteristic                              | Total (N=750) | Patients With SSS (n=35) | Patients Without SSS (n=715) | P Value |
|---------------------------------------------|---------------|--------------------------|-----------------------------|---------|
| MV surgery, n (%)                           |               |                          |                             | 0.098   |
| MV repair                                   | 304 (40.5)    | 9 (25.7)                 | 295 (41.3)                  |         |
| MV replacement                              | 446 (59.5)    | 26 (74.3)                | 420 (58.7)                  |         |
| Concomitant TV surgery, n (%)               | 402 (53.6)    | 25 (71.4)                | 377 (52.7)                  | 0.046   |
| Concomitant CABG, n (%)                     | 60 (8.0)      | 4 (11.4)                 | 56 (7.8)                    | 0.655   |
| CPB time, min                               | 167.2±55.2    | 195.6±55.4               | 165.8±54.8                  | 0.002   |
| Cross-clamp time, min                       | 108.7±45.5    | 124.2±41.3               | 108.0±45.6                  | 0.040   |

#### Maze procedure, n (%)

| Characteristic                              | Total (N=750) | Patients With SSS (n=35) | Patients Without SSS (n=715) | P Value |
|---------------------------------------------|---------------|--------------------------|-----------------------------|---------|
| Bilateral maze                              | 513 (68.4)    | 32 (91.4)                | 481 (67.3)                  | 0.005   |
| Cryoablation                                | 721 (96.1)    | 35 (100.0)               | 686 (95.9)                  | 0.478   |
| Concomitant LA appendage resection/obliteration | 315 (42.0) | 16 (45.7)                | 299 (41.8)                  | 0.779   |
| Concomitant LA volume reduction             | 221 (29.5)    | 13 (37.1)                | 208 (29.1)                  | 0.406   |

#### Discharge medication, n (%)

| Characteristic                              | Total (N=750) | Patients With SSS (n=35) | Patients Without SSS (n=715) | P Value |
|---------------------------------------------|---------------|--------------------------|-----------------------------|---------|
| Amiodarone                                  | 117 (15.6)    | 3 (8.6)                  | 114 (15.9)                  | 0.241   |
| Other antiarrhythmics                       | 5 (0.7)       | 0 (0)                    | 5 (0.7)                     | 0.787   |

Data are given as mean±SD unless otherwise indicated. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; OHS, open-heartsurgery; PG, pressure gradient; RA, right atrial; SSS, sick sinus syndrome; TR, tricuspid regurgitation; TV, tricuspid valve.
Table 2. Predictors of Development of SSS After MVS and MP

| Variable                        | Univariable Analysis | Multivariable Analysis |
|--------------------------------|----------------------|------------------------|
|                                | HR 95% CI            | P Value                | HR 95% CI          | P Value          |
| Rheumatic cause of mitral disease | 0.84 0.43–1.63       | 0.597                  | ...               | ...              |
| Biatrial maze (vs LA maze)      | 5.37 1.64–17.57     | 0.005                  | 3.58 1.08–11.86   | 0.037            |
| Age, per 10 y                   | 1.07 1.04–1.11       | <0.001                 | 1.75 1.26–2.43    | <0.001           |
| Moderate-to-severe TR           | 2.65 1.35–5.22       | 0.005                  | ...               | ...              |
| TR PG, per 10 mm Hg             | 1.03 1.01–1.05       | 0.003                  | 1.24 1.02–1.50    | 0.032            |
| RA area, per mm²                | 1.03 1.00–1.05       | 0.033                  | ...               | ...              |

CI indicates confidence interval; HR, hazard ratio; LA, left atrial; MVS, mitral valve surgery; PG, pressure gradient; RA, right atrial; SSS, sick sinus syndrome; TR, tricuspid regurgitation.

Table 3. Characteristics of Study Patients With or Without Rheumatic Pathological Features

| Characteristics                        | RHD (n=431) | No RHD (n=319) | P Value |
|----------------------------------------|-------------|----------------|---------|
| Age, y                                  | 55.6±11.6   | 58.5±12.9      | 0.002   |
| Men, n (%)                             | 127 (29.5)  | 189 (59.2)     | <0.001  |
| LV end-diastolic dimension, mm         | 51.9±7.4    | 58.3±9.8       | <0.001  |
| LA size, mm²                           | 58.3±9.2    | 56.4±9.9       | 0.006   |
| LA area, mm²                           | 47.1±15.6   | 43.4±14.8      | 0.001   |
| RA area, mm²                           | 25.3±10.0   | 26.4±11.4      | 0.184   |
| LV ejection fraction, %                | 54.7±7.7    | 58.4±9.2       | <0.001  |
| Moderate-to-severe MS, n (%)           | 298 (69.1)  | 9 (2.8)        | <0.001  |
| Moderate-to-severe MR, n (%)           | 210 (48.7)  | 313 (98.1)     | <0.001  |
| TR PG, mm Hg                           | 38.0±13.6   | 38.9±16.4      | 0.421   |
| MV surgery, n (%)                      |             |                |         |
| MV repair                              | 45 (10.4)   | 259 (81.2)     | <0.001  |
| MV replacement                         | 386 (89.6)  | 60 (18.8)      |         |
| Concomitant TV surgery, n (%)          | 243 (56.4)  | 159 (49.8)     | 0.089   |
| CPB time, min                          | 106.0±51.3  | 112.5±36.2     | 0.043   |
| Cross-clamp time, min                  | 158.3±51.8  | 179.3±57.4     | <0.001  |
| Bialtrial maze, n (%)                  | 213 (66.8)  | 300 (96.6)     | 0.456   |
| Cryoablation, n (%)                    | 415 (96.3)  | 306 (95.9)     | 0.408   |
| Concomitant LA appendage resection/obliteration, n (%) | 218 (50.6) | 97 (30.4) | <0.001 |
| Concomitant LA volume reduction, n (%) | 135 (31.3)  | 86 (27.0)      | 0.224   |

Data are given as mean±SD unless otherwise indicated. CPB indicates cardiopulmonary bypass; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; PG, pressure gradient; RA, right atrial; RHD, rheumatic heart disease; TR, tricuspid regurgitation; TV, tricuspid valve.

underwent the biatrial MP and the remaining patients underwent the LA MP (n=206, 43.7%). The frequencies of concomitant TV repair in patients who underwent the biatrial MP and the LA MP were 46.6% and 8.3%, respectively. Those who underwent the biatrial MP had a higher mean age, larger LA and RA areas, and longer cardiopulmonary bypass and cross-clamp times (Table 4). In the overall population, patients who underwent bialtrial maze surgery were at a higher risk of SSS development than those who underwent LA maze surgery (6.1±1.2% versus 1.4±0.8%; P=0.002; Figure 5A). Among patients without moderate-to-severe TR, the 4-year incidence of SSS development was higher after the biatrial MP than after the LA MP (4.6±1.4% versus 1.0±0.7%; P=0.023; Figure 5C), whereas the incidence of recurrent AF did not reach statistical significance (Figure 5D). After adjustment for baseline characteristics by propensity scoring using the inverse probability of treatment weighting method (Table 5), patients who underwent the biatrial MP showed a higher risk of SSS development (HR, 4.79; 95% CI, 1.62–14.15; P=0.005) than those who underwent the LA MP. However, the risk of recurrent AF did not reach statistical significance (HR, 1.31; 95% CI, 0.87–1.99; P=0.200). Of the patients with moderate-to-severe TR (n=278, 37.0%), most (n=261, 93.9%) underwent TV surgery (ie, either TV replacement [n=17] or TV repair [n=244]). In this group, the biatrial MP was concurrently performed for most patients (n=247, 88.8%), and the lesion extent of the MP revealed no difference in the rates of SSS development and recurrent AF (Figure 5E and 5F).

Efficacy of the MP

Early recurrence of AF during the 90-day blanking period was documented in 275 patients (36.7%). After the blanking period, AF recurrence was observed in 186 patients (24.8%) during follow-up, with the 4-year incidence rate of AF recurrence being 22.9%. The rate of recurrent AF was higher in patients who underwent the biatrial MP than in those who
underwent the LA MP alone (28.2 ± 2.3% versus 17.6 ± 2.7%; \( P = 0.002 \); Figure 5B). However, in multivariate adjustment, the lesion extent of the MP was not an independent factor associated with AF recurrence (HR, 1.19; 95% CI, 0.82–1.74; \( P = 0.352 \); Table 6).

**Discussion**

This retrospective analysis focused primarily on the safety outcomes of the MP performed concomitantly with MVS and revealed the presence of an ongoing and cumulative risk of SSS development during follow-up after the index surgical procedure. The development of symptomatic bradycardia exhibited a characteristic temporal pattern on the basis of the type: SSS was the dominant form in the late postoperative period, whereas AVB was confined to the early postoperative period. The underlying cause of MV disease did not affect SSS development, and the biatrial MP was found to be an independent predictor of SSS development without any advantage of preventing AF recurrence, especially in patients without moderate-to-severe TR.

**SSS After MVS and the MP**

Most previous studies have focused on the efficacy of the MP; therefore, data about safety outcomes, especially the natural course from a chronological viewpoint, are lacking, even in a recently published study on late outcomes. The limited data available on SSS development after the procedure demonstrate marked variations in the frequency of SSS development ranging from 6.8% to 21.5%. Some studies included a relatively small numbers of patients (<300), and the reported incidence of SSS was usually the secondary outcome, outside the main findings. In a recently published long-term follow-up study on 320 patients with a mean follow-up time of 111 ± 44 months after the Cox-maze III procedure, pacing-dependent rhythm was observed in 10.6%; and among them, the prevalences of atrial, ventricular, and dual-chamber pacing were 6%, 1.6%, and 3% of patients, respectively. The frequency of pacing-dependent rhythm at a 4-year follow-up duration after MVS and the MP in our study was 4.1%; and differing follow-up durations can explain the differing frequencies of pacing-dependent rhythm, which may reflect the

**Figure 4.** Time-to-event curves showing the impact of rheumatic pathological features on clinical outcomes. Patients with rheumatic mitral valve disease were not at a higher risk of sick sinus syndrome development (A), permanent pacemaker implantation (B), recurrent atrial fibrillation (AF; C), or composite clinical outcomes (death, stroke, and rehospitalization; D).
importance of follow-up duration in representing the ongoing risk of symptomatic bradyarrhythmia development after the MP.

Another variable to be considered in interpreting the frequency of SSS development was the underlying cardiac disease that needed a concomitant procedure. In a study with the longest follow-up duration,21 MVS was performed only in 7% of patients, and 6% of patients underwent concomitant coronary artery bypass grafting. Thus, most patients underwent the MP alone. We excluded patients who underwent concomitant aortic valve surgery or the MP alone without MVS, thereby maintaining the homogeneity of the study subjects. To date, it is not known whether additional surgical procedures, such as mitral or aortic valve surgery, can contribute to an increased risk of SSS development after the MP. Further investigations using a more homogeneous patient population are necessary.

In addition to the ongoing risk of SSS development, our data revealed different temporal developmental patterns in SSS and AVB. Previous surgical series have demonstrated a predominance of AVB as an indication of PPM implantation in the early postoperative period,4,9 and SSS development after the MP has not been adequately evaluated. In our study, SSS development was confirmed to be a more frequently encountered complication of the MP than AVB. This difference can be easily explained by the longer follow-up period of our study. The aging process itself is the main risk factor of sinus node dysfunction via the common mechanism of degeneration and fibrosis of the conduction system.22,23 In a subgroup analysis of our data, 20 patients developed SSS >3 months after the surgery (late-onset group) and 15 patients developed SSS <3 months after the surgery (early-onset group). The late-onset group had a significantly higher mean age (67.3±7.3 versus 59.9±9.9 years; P=0.015), which suggested that age has an impact on the ongoing or cumulative risk of SSS development. Interestingly, some previous studies have described sinus node dysfunction from surgical damage as a transient phenomenon confined to the immediate postoperative period.24,25 However, considering that surgery in the right atrium inevitably causes tissue damage and can alter the conduction system to some degree, a biatrial maze lesion set can make a substrate of conduction disturbance that can evolve into SSS development.12 The contribution of these 2 potential mechanisms, aging and the substrate associated with surgical trauma, could be a plausible explanation for the difference in the frequency of SSS development after biatrial

| Characteristic | Biatrial Maze (n=266) | LA Maze (n=206) | P Value |
|----------------|-----------------------|----------------|---------|
| Age, y         | 56.3 ±11.5            | 52.4 ±13.1     | 0.001   |
| Men, n (%)     | 142 (53.4)            | 96 (46.6)      | 0.171   |
| LV end-diastolic dimension, mm | 55.2±9.2 | 55.4±9.1 | 0.861 |
| LA size, mm    | 57.7±9.2              | 54.6±7.7       | <0.001 |
| LA area, mm²   | 45.6±14.6             | 42.8±11.3      | 0.020   |
| RA area, mm²   | 23.0±8.1              | 21.1±7.5       | 0.007   |
| LV ejection fraction, % | 56.4±8.5 | 56.4±9.2 | 0.941 |
| Moderate-to-severe MS, n (%) | 169 (60.2) | 121 (58.7) | 0.829 |
| Moderate-to-severe MR, n (%) | 189 (71.1) | 140 (68.0) | 0.533 |
| Rheumatic disease, n (%) | 140 (52.6) | 108 (52.4) | 0.445 |
| TR PG, mm Hg   | 35.6±12.2             | 33.4±12.3      | 0.054   |

MV surgery, n (%)

| MV repair | 120 (45.1) | 88 (42.7) | 0.670 |
| MV replacement | 146 (54.9) | 118 (57.3) | 0.001 |
| Concomitant TV surgery, n (%) | 124 (46.6) | 17 (8.3) | <0.001 |
| CPB time, min | 111.0±34.7 | 96.3±32.0 | <0.001 |
| Cross-clamp time, min | 173.8±54.7 | 149.4±52.3 | <0.001 |
| Cryoablation, n (%) | 260 (97.7) | 193 (93.7) | 0.035 |
| Concomitant LA appendage resection/obliteration, n (%) | 123 (46.2) | 70 (34.0) | 0.010 |
| Concomitant LA volume reduction, n (%) | 85 (32.0) | 27 (13.1) | <0.001 |

Data are given as mean±SD unless otherwise indicated. CPB indicates cardiopulmonary bypass; LA, left atrial; LV, left ventricular; MP, maze procedure; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; PG, pressure gradient; RA, right atrial; TR, tricuspid regurgitation; TV, tricuspid valve.

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versus LA MP during the follow-up period, with SSS being a predominant indication of PPM implantation in the late postoperative period. The absence of any impact of rheumatic pathological features on SSS development suggested that surgical injury is more powerful than a presurgical substrate change.

Another interesting finding in our study is that the effect of lesion extent of the MP on development of SSS is dependent on underlying TR severity. It has been well recognized that severe TR does not necessarily regress after MVS, and persistence or development of late significant TR after uneventful MVS with its poor long-term clinical and surgical outcome remains a challenging issue. Because AF has been proved to be an important risk factor of development of late significant TR and the beneficial effect of the MP to prevent late TR development after MVS has been
confirmed,35,36 the MP has been more widely performed during MVS. In addition, some surgeons believe that remodelling annuloplasty of the TV on the basis of tricuspid dilation improves functional status irrespective of the TR grade.37 A concomitant TV repair during MVS in patients without moderate-to-severe TR is still controversial, and the current guidelines do not provide definite recommendations on TV repair for these patients.38 Furthermore, the alleged benefits of TV repair in this select group of patients include a decreased rate of congestive heart failure or TR progression; however, the benefits in terms of hard end points have not been evident.13 Thus, our finding of an increased SSS development without additional benefits, especially after adjustment, suggested that the “routine” RA MP was not helpful in patients with mild or no TR. This finding is in line with the results of a recent randomized trial in which an additional RA MP failed to show a better rhythm control rate (66% in the biatrial maze group versus 61% in the LA maze group).4 In a recent meta-analysis of 10 randomized and observational studies, the rhythm control rate up to 1 year

| Variable | Biatrial Maze (n=266) | LA Maze (n=206) | SMD Before Weighting | SMD After Weighting |
|----------|------------------------|------------------|----------------------|---------------------|
| Age, y   | 56.3 ±11.5             | 52.4 ±13.1       | 0.319                | 0.003               |
| Men, n (%) | 142 (53.4)            | 96 (46.6)        | 0.136                | 0.015               |
| Body mass index, kg/m² | 23.6 ±3.4          | 23.8 ±3.2        | 0.051                | 0.010               |
| Hypertension | 152 (48.9)         | 226 (49.9)       | 0.187                | 0.004               |
| Diabetes mellitus | 19 (7.1)            | 9 (4.4)          | 0.119                | 0.001               |
| CHF, n (%) | 21 (7.9)              | 14 (6.8)         | 0.042                | 0.004               |
| Previous CVA, n (%) | 9 (3.4)              | 10 (4.9)         | 0.074                | 0.001               |
| Previous CAD, n (%) | 17 (6.4)             | 7 (3.4)          | 0.139                | 0.001               |
| Previous OHS, n (%) | 16 (6.0)             | 6 (2.9)          | 0.150                | 0.001               |
| Rheumatic pathological feature, n (%) | 140 (52.6)         | 108 (52.4)       | 0.015                | 0.012               |
| LA area, mm² | 45.6±14.6            | 42.8±11.3        | 0.213                | 0.025               |
| RA area, mm² | 23.0±8.1             | 21.1±7.5         | 0.253                | 0.015               |
| LV ejection fraction, % | 56.4±8.5             | 56.4±9.2         | 0.007                | 0.008               |
| TR PG, mm Hg | 35.6±12.2            | 33.4±12.3        | 0.194                | 0.021               |
| Moderate-to-severe MS, n (%) | 169 (60.20)         | 121 (58.7)       | 0.029                | 0.010               |
| Moderate-to-severe MR, n (%) | 189 (71.1)           | 140 (68.0)       | 0.067                | 0.013               |

Data are given as mean±SD unless otherwise indicated. CAD indicates coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; OHS, open-heart surgery; PG, pressure gradient; RA, right atrial; SMD, standardized mean difference; TR, tricuspid regurgitation.

### Table 6. Predictors of Recurrent AF After MVS and MP

| Variable                             | Univariable Analysis | Multivariable Analysis |
|--------------------------------------|----------------------|------------------------|
|                                      | HR 95% CI            | P Value                |
|                                      | HR 95% CI            | P Value                |
| Age, per 10 y                        | 1.29 1.14–1.46       | <0.001                 |
|                                      | 1.22 1.08–1.39       | 0.002                  |
| Men                                  | 0.70 0.52–0.95       | 0.023                  |
|                                      | 0.77 0.56–1.05       | 0.102                  |
| Hypertension                         | 1.33 0.98–1.82       | 0.069                  |
|                                      | ...                  | ...                    |
| Diabetes mellitus                    | 1.48 0.94–2.31       | 0.087                  |
|                                      | ...                  | ...                    |
| Left atrial area, per mm²            | 1.01 1.01–1.02       | 0.001                  |
|                                      | 1.01 1.00–1.02       | 0.008                  |
| Right atrial area, per mm²           | 1.02 1.01–1.04       | <0.001                 |
|                                      | 1.01 1.00–1.03       | 0.114                  |
| Moderate-to-severe tricuspid regurgitation | 1.88 1.41–2.51   | <0.001                 |
|                                      | 1.37 0.98–1.92       | 0.070                  |
| Lesion extent (biatrial vs left atrial maze) | 1.71 1.21–2.40 | 0.002                  |

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; MP, maze procedure; MVS, mitral valve surgery.
was superior in the biatrial maze group, but was inconclusive after that period, whereas the PPM rate representing SSS development was definitely higher in the biatrial maze group than in the LA maze group (7.0% versus 5.5%; HR, 1.75; 95% CI, 1.16–2.66; P=0.008).  

Limitations
Because this was a retrospective observational study conducted at a single center, selection bias was possible. Technical revolutions in MPs during the study period of >10 years and the nonrandomization of MPs and TV repair are inherent limitations of this study. However, because clinical events, such as hospital admission or mortality, could be assessed and baseline and follow-up clinical data, such as echocardiographic, electrophysiographic, and Holter recordings of all patients, were available for analysis, we believe that our main findings are valid despite these limitations. There was continuous technical advancement in the details of the MP, such as posterior box lesion for AF ablation of the Cox-maze IV procedure. 

Conclusions
Patients who underwent MVS and a concomitant MP have an ongoing cumulative risk of SSS development, with a higher risk of adverse clinical events, and this should be considered an inherent limitation of a retrospective study.

Disclosures
None.

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