Alternative Energy Sources for Surgical Treatment of Atrial Fibrillation in Patients Undergoing Mitral Valve Surgery: Microwave Ablation vs Cryoablation

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INTRODUCTION
The maze procedure described by Cox (1, 2) is an accepted, effective therapeutic option for patients with atrial fibrillation (AF). In recent years, the conventional cut-and-sew Cox Maze procedure has been replaced by other procedures using alternative energy sources such as radiofrequency, microwaves, ultrasound, laser, and cryothermia to rapidly produce maze lesion sets with minimal risk of bleeding (3-5). Several studies have investigated the effectiveness of these energy sources and have shown varying results in terms of restoration of sinus rhythm (6).

However, previous comparative analyses of clinical outcomes according to different energy sources have had limitations, including short follow-up durations (<1 yr) and small patient populations (6-9). Furthermore, different definitions of procedural success may have contributed to the difficulties in interpreting or comparing the reported outcomes.

We therefore compared the long-term clinical outcomes of maze procedures using microwave ablation or cryoablation in patients with mitral disease and AF. In reporting the rhythm outcomes, we followed the consensus of reporting standards made by the Heart Rhythm Society Task Force on Catheter and Surgical Ablation of AF (10).

MATERIALS AND METHODS
Patients
Between January 1999 and January 2005, 340 consecutive patients underwent a mitral valve operation and concomitant maze procedure involving microwave ablation (n=96, MW group) or cryoablation (n=244, Cryo group) by a single cardiac surgeon in Asan Medical Center, Seoul, Korea. This patient population includes 158 patients (46.5%) who were analyzed in a previous report regarding the influence of mitral valve function on AF recurrence after mitral repair and maze procedure (11). Further follow-up data from the patients included in the previous study, and the addition of data from mitral replacement patients formed the subject of the present study to focus on the comparison between cryoablation and microwave ablation.

Surgical techniques
Myocardial protection was achieved with antegrade and retrograde tepid blood cardioplegia. After aortic cross-clamping, mitral valve exposure was obtained by a left atrial (LA) incision. A modified version of the Cox Maze III procedure was performed, the details of which have been described previously (12). Cryoablation was applied at -60°C with a 15-degree-angled, 30-mm or 70-mm long freeze tip with a diameter of 9 mm (Frigitronics...
Cardiac Cryosurgical System 200; Frigitronics, Inc, Coopersurgical, Shelton, CT, USA). The probe was usually applied for 2 min. Microwave energy was applied endocardially using FLEX 4 microwave ablation probes (Afx Inc, Fremont, CA, USA). The energy level used was 65 watts and duration of ablation was 2 min. LA size was reduced by generous resection of redundant atrial tissue off the posterior LA wall parallel to the posterior mitral annulus. During the study period, the lesion set of ablation procedure was maintained uniformly regardless of energy sources used.

Echocardiography and rhythm follow-up

Preoperative echocardiography (both transthoracic and transesophageal) was performed in all patients (within 2 months before surgery). Transthoracic echocardiographic evaluation was performed at 3 and 6 months and every year thereafter. All patients underwent two-dimensional echocardiography and Doppler color-flow imaging using a Hewlett-Packard Sonos 2500 or 5500 imaging system equipped with a 2.5-MHz transducer (Hewlett-Packard, Andover, MA, USA).

During postoperative hospitalization, each patient’s rhythms were assessed daily using standard 12-channel surface electrocardiography (EKG). Follow-up EKGs were performed at 3–6-month intervals during the first 2 yr and every year thereafter. Any AF events during the initial post-ablation blanking period of 3 months were defined as “early events.” Failure of the maze procedure included any recurrent AF, atrial tachycardia, or atrial flutter at least 3 months after stopping amiodarone treatment ("late event"). The results are presented in ‘Freedom from AF without antiarrhythmic agent’ (10).

All data were collected prospectively and stored for later analysis in a specially designed and regimented database.

Postoperative management

Indications for amiodarone treatment included: failure of postoperative sinus conversion, persistent AF, atrial tachycardia, frequent atrial premature beat and recurrent atrial tachyarrhythmia. Amiodarone was commenced at 1,200 mg/day and tapered within 1 or 2 weeks. Patients who underwent valve repair or bioprosthesis valve implantation were routinely administered anticoagulant therapy with warfarin for 3–6 months postoperatively, with a target international normalized ratio (INR) of 1.5–2.5 at the discretion of the attending surgeon. Maintenance of anticoagulation therapy thereafter was determined according to the presence of thromboembolic risks and cardiac rhythm status in each patient.

Statistics

Categorical variables are presented as frequencies and percent ages, and were compared using the chi-square test or Fisher’s exact test. Continuous variables are expressed as mean±SD or medians with ranges, and were compared using the Student’s unpaired t-test or the Mann-Whitney U test, as appropriate. Kaplan-Meier curves were employed to delineate freedom from AF, and log-rank test was used to compare the differences in AF-free rates between groups.

To reduce the impact of treatment selection bias and potential confounding in an observational study, we performed rigorous adjustment for significant differences in patient characteristics by using inverse-probability-of-treatment weighting (IPTW) (13, 14). With that technique, weights for patients receiving microwave ablation were the inverse of (1 minus propensity score), and weights for patients receiving cryoablation were the inverse of propensity score. The propensity scores were estimated by multiple logistic-regression analysis (14). All prespecified covariates were included in full nonparsimonious models for microwave ablation versus cryoablation (Tables 1, 2). The discrimination and calibration abilities of each propensity score model were assessed by C statistics and the Hosmer-Lemeshow test. The model was well calibrated (Hosmer-Lemeshow test; P = 0.866) with reasonable discrimination (C statistic=0.702).

For multivariate analyses, the Cox proportional hazards model was fitted with time to AF recurrence. Variables with a probability value ≤0.20 in univariate analyses were candidates for the model.

Table 1. Preoperative profiles of patients

| Variables | Cryo group | MW group | P value |
|-----------|------------|----------|---------|
| Number of patients | 244 | 96 |     |
| Age (yr) | 49.7±12.1 | 50.7±13.5 | 0.514 |
| Female gender, n (%) | 154 (63.1) | 54 (56.2) | 0.242 |
| Diabetes mellitus, n (%) | 16 (6.6) | 9 (9.4) | 0.304 |
| Hypertension, n (%) | 20 (8.2) | 6 (6.3) | 0.654 |
| History of thromboembolism, n (%) | 29 (11.9) | 9 (9.4) | 0.571 |
| Cardiac ratio, % | 60.1±7.2 | 58.3±11.5 | 0.158 |
| Previous cardiac surgery, n (%) | 20 (8.2) | 4 (4.2) | 0.243 |
| Causes of MV disease, n (%) | 174 (71.3) | 53 (55.2) | 0.005* |
| Rheumatic | 70 (28.7) | 43 (44.8) |     |
| Degenerative |     |
| Mode of MV disease, n (%) | 123 (50.4) | 60 (62.5) | 0.139 |
| Predominant mitral regurgitation |     |
| Predominant mitral stenosis | 72 (29.3) | 20 (20.8) |     |
| Mixed stenoregurgitation | 45 (18.4) | 13 (13.5) |     |
| Prosthetic valve failure | 4 (1.6) | 3 (3.1) |     |
| Echocardiographic data |     |
| LV ejection fraction (%) | 55.0±10.1 | 55.8±10.1 | 0.468 |
| LA dimension (mm) | 60.9±9.5 | 60.5±10.6 | 0.735 |
| LV end systolic diameter (mm) | 40.4±8.5 | 40.2±8.7 | 0.812 |
| LV end diastolic diameter (mm) | 58.3±9.7 | 58.5±9.9 | 0.808 |
| AF profiles |     |
| AF duration (yr) | 5.7±6.8 | 5.7±7.2 | 0.977 |
| Finé (<1 mm) AF wave, n (%) | 116 (47.5) | 49 (51.0) | 0.561 |
| AF type, n (%) |     |
| Paroxysmal | 20 (8.2) | 13 (13.5) | 0.240 |
| Persistent (<1 yr) | 41 (16.8) | 12 (12.5) |     |
| Longstanding persistent (≥1 yr) | 183 (75.0) | 71 (74.0) |     |

Data represent mean±SD. *P<0.05.

MV, mitral valve; LV, left ventricle; LA, left atrium; AF, atrial fibrillation.
multivariable models. Multivariate analyses involved a backward elimination technique and only variables with a P value of <0.10 were used in the final model. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance. SAS software, version 9.1 (SAS Institute, Cary, NC, USA) and SPSS version 12 were used for the statistical analysis.

This study was approved by our institutional review board (IRB No. 2008-0638). The informed consent was waived by the board because of the retrospective nature of our study.

RESULTS

Mean age at the time of operation was 50.0±12.5 yr, and 208 (61.2%) patients were female. There were seven early deaths. Among the early survivors (n=333), follow-up EKG analysis beyond 12 months postoperation was possible in 319 patients (95.8%); this analysis was not possible in 4 patients due to death within 12 months and 10 patients who were lost to follow-up. The mean follow-up period was 46.1±28.2 months.

Preoperative patient characteristics are listed in Table 1. Patients in the Cryo group were more likely to have rheumatic MV disease than those in the MW group, significantly. Otherwise, the two groups were similar in terms of preoperative patient demographic profiles, clinical features of mitral valve disease and AF, and preoperative echocardiographic data.

The aortic clamping time was significant longer in the Cryo group than the MW group (Table 2). There were no significant between-group differences in other operative parameters including duration of cardiopulmonary bypass, type of mitral valve procedure and concomitant cardiac procedure (Table 2). There were four cases of late stroke (1.2%) and seven late deaths (2.1%; Table 3). Overall 3-yr and 5-yr survival rates were 96.1±1.1% and 95.6±1.2%, respectively. Three patients (0.9%) failed to regain normal sinus rhythm and nine patients (2.6%) required permanent pacemaker implantation. The rates of sinus rhythm restoration and rhythm at last follow-up were similar for the two groups (Table 3).

Ninety patients (26.5%) experienced early AF events (58 in the Cryo group and 32 in the MW group, P=0.320). Sixty patients (17.6%) experienced late AF recurrence during the follow-up period (43 in the Cryo group and 17 in the MW group, P=0.755). All of these 60 patients with late AF recurrence received amiodarone medication, which resulted in sinus rhythm conversion in all patients. Of them, 32 experienced AF recurrence after discontinuation of amiodarone medication, and subsequently restarted the amiodarone medication. None of the patients who experienced late AF recurrence progressed to persistent AF. An additional 21 patients had received amiodarone medication since the early postoperative period and 14 of these patients eventually discontinued amiodarone therapy without experiencing late AF recurrence. Other three patients had been receiving amiodarone at the time of analysis but without experiencing AF recurrence.

Table 2. Operative procedures

| Operation types                       | Cryo group (n=244) | MW group (n=96) | P value |
|---------------------------------------|--------------------|----------------|---------|
| Cardiopulmonary bypass time (min)     | 163.7±50.4         | 164.7±36.4     | 0.850   |
| Aorta cross clamping time (min)       | 119.5±34.0         | 109.2±28.6     | 0.005*  |
| Type of mitral valve procedure, n (%) |                    |                |         |
| Repair                                | 131 (53.7)         | 57 (59.4)      | 0.342   |
| Replacement                           | 113 (46.3)         | 39 (40.6)      |         |
| Concomitant tricuspid valve repair, n (%) | 120 (49.2)       | 48 (50.0)      | 0.892   |
| Other cardiac co-operation            | 0.447              |                |         |
| None                                  | 184 (75.4)         | 74 (77.1)      |         |
| Aortic valve surgery                  | 39 (16.0)          | 14 (14.6)      |         |
| Coronary artery bypassing             | 17 (7.0)           | 2 (2.1)        |         |
| Others                                | 8 (3.3)            | 6 (6.3)        |         |

Data represent mean±SD.

*P<0.05; †Four patients underwent aortic valve surgery plus coronary artery bypassing.

Table 3. Operative outcomes

| Outcomes                       | Cryo group | MW group | P value |
|-------------------------------|------------|----------|---------|
| Early mortality, n (%)        | 5 (2.0)    | 2 (2.1)  | >0.999  |
| Late mortality, n (%)         | 5 (2.0)    | 2 (2.1)  | >0.999  |
| Stroke, n (%)                 | 3 (1.2)    | 1 (1.0)  | >0.999  |
| Sinus conversion date, days   | 1.2±6.5    | 0.4±1.9  | 0.149   |
| Recent follow up rhythm, n (%)| 210 (86.1) | 79 (82.3) | 0.531   |

Data represent mean±SD. *P<0.05.

http://jkms.org 1469

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Overall unadjusted 3-yr, 5-yr and 7-yr AF-free rates in patients who did not receive antiarrhythmic agents were 85.9±2.1%, 78.1±2.9% and 70.2±4.4%, respectively. The MW group had a greater tendency of AF-recurrence rate than the Cryo group (Fig. 1). After adjustment for baseline patients’ characteristics with IPTW, the MW group only showed a tendency toward more frequent AF recurrence than the Cryo group (Hazard ration 1.66, 95% confidence interval 0.89 to 3.07). Univariate and multivariate analyses revealed that older patient age (P<0.001) and greater LA size (P<0.001) were independent factors for late AF recurrence (Table 4).

Transmitral A-wave prevalence and velocity plots are shown in Figs. 2, 3, respectively. There were no significant differences in transmitral A-wave prevalence and velocity between groups at each postoperative time point.

Table 4. Univariate and multivariate analyses for late atrial fibrillation recurrence

| Variables                                | Univariate P value | Multivariate HR 95.0% C.I. P value |
|-------------------------------------------|-------------------|-----------------------------------|
| Age (yr)                                  | 0.004*            | 1.04 1.02–1.06 <0.001*            |
| Diabetes mellitus                         | 0.045*            |                                   |
| Cardiacoracic ratio                       | 0.018*            |                                   |
| Left ventricular ejection fraction        | 0.166             |                                   |
| Left atrial dimension                     | <0.001*           | 1.06 1.03–1.08 <0.001*            |
| AF duration                               | 0.002*            |                                   |
| Fine (<1 mm) AF wave                      | 0.007*            |                                   |
| AF type (paroxysmal vs persistent)        | 0.070             |                                   |
| Concomitant tricuspid valvuloplasty       | 0.046*            |                                   |
| Energy source (cryoablation vs. microwave)| 0.089*            |                                   |

Fig. 2. Transmisral A-wave prevalence (%). Inter-group comparisons of A-wave prevalence show no differences during the postoperative period (P values ranged from 0.18 to 1.0 for each postoperative point).

Fig. 3. Transmitral peak A-wave velocity (cm/sec). Inter-group comparisons of A-wave velocity show no differences during the postoperative period (P values ranged from 0.16 to 0.84 for each postoperative point).

**DISCUSSION**

Alternative energy sources are being increasingly used in the field of AF ablation surgery owing to their convenience in application, shorter procedural time and minimal risk of postoperative bleeding. Endocardial ablations have demonstrated a 70–80% long-term success rate when used together with other open heart procedures. Progress has focused on rapidly, efficiently, and safely creating therapeutic ablative lesions without incision. Delivery systems are designed to be precise, flexible and able to access any anatomic location. Owing to the development of these delivery systems, AF ablation surgery has evolved to become an endoscopic, off-pump, robotically assisted successful procedure for the treatment of AF (6).

Cryoablation was the first alternative approach to be used in AF ablation surgery (15), and thus has the advantage that it is the most time-tested and has a well-characterized safety profile. Several studies have reported long-term results of cryoablation for treatment of AF and have shown that it has similar results as the conventional ‘cut and sew’ Cox Maze procedure in terms of restoration and maintenance of sinus rhythm (16–18).

Microwave ablation has several advantages, in that, shielded probes enable a minimally invasive off-pump epicardial approach, potentially no cardiac ischemic time requirement, better handling of anatomic variation, avoidance of a left atriotomy, and a less risk of pulmonary vein stenosis (19). It can accommodate a variety of lesion sets. However, in contrast to cryoablation, most studies have recorded follow-up rhythm data after microwave ablation for less than 1 yr (6-9). Determining the clinical effectiveness of AF ablation therapy based on 1 yr follow-up data seems inadequate, particularly because in 2007 the Heart Rhythm Society Task Force on Catheter and Surgical Ablation of AF recommended that all patients in a clinical investigation
should be followed for a minimum of 12 months (10). To our knowledge, only one study has investigated the long-term (>1 yr) outcomes of left atrial endocardial microwave ablation (20). In this previous study, 41 patients were enrolled and the mean duration of postoperative follow-up was 5.37±0.91 yr. After 5 yr, only 39.3% of patients were in sinus rhythm. The investigators concluded that microwave ablation is not a reliable method for achieving long-term conversion to sinus rhythm. Although the AF ablation procedure used in this previous study was not a biatrial full maze procedure, the results were significant because they were the first reported data on the long-term outcomes of microwave ablation and because they were quite different from previous relatively short-term data indicating that the technique is excellent (7-9). The authors suggested that an important reason for the modest conversion rate to sinus rhythm in their study was a lack of lesion transmurality.

In support of their hypothesis, a postmortem histologic study was conducted in which three patients underwent microwave ablation for the treatment of AF (21). All three patients had immediate successful sinus rhythm restoration, and autopsies performed within 22 days of surgery showed that in most tissue samples, the lesions were not transmural and the extent of myocardial damage was highly variable.

In the present study, the analyses showed a trend toward favoring the use of cryoablation than the microwave ablation in terms of the restoration and maintenance of sinus rhythm during a long-term follow-up. This difference in late outcomes has not been reported previously. Although histologic examinations of ablated atrial tissue were not performed in this study, we assume the differences in long-term rhythm outcomes between microwave and cryoablation are due to differences in the ability to produce transmural necrosis, in agreement with a previous proposal (20). Application of a nitrous-oxide-based cryoablation probe at -60°C to atrial tissue for 2 min creates a transmural lesion that can be visually verified (22). However, the current microwave ablation approach lacks a transmural feedback mechanism, making it difficult to verify the transmural necrosis during the procedure.

In the present study, the microwave energy level used was 65 watts and the duration of ablation was 2 min per lesion; this level of energy delivery is above the level which has been suggested and used by other researchers. Tissue shrinking of lesion lines on endocardial surface with dark yellow discoloration could be observed following the procedure and this finding was regarded as the indication of satisfactory injury in our practice. If the microwave energy is applied endocardially, most researchers use an energy power of 40 watts and an ablation time of 25 sec per lesion at a frequency of 2.45 GHz (9, 23). One research group (24) proposed 65 watts and 60 seconds of ablation time per lesion, and this energy level is also recommended by the device manufacturer for ‘epicardial’ application of microwave energy for beating-heart AF ablation (25). However, to investigate the long-term rhythm outcome, we suggest that the level of energy and the duration of ablation should be evaluated and determined according to the long-term rhythm status in the clinical setting. Further investigations are needed to address this issue.

In this study, the aortic clamping time was longer in the Cryo group than the MW group. When a microwave probe is applied, it takes about 2 min to create each linear lesion, whereas cryoablation takes 2 min of freezing plus about 20 sec of warming. Furthermore, the flexible nature of microwave probes makes it easier to rapidly generate the lesions, so additional time can be saved.

This study is subject to the limitations inherent to retrospective observational studies. Although the analyses showed a definite trend toward favoring the use of cryoablation than the microwave ablation in terms of freedom from AF, the results were statistically marginal. Studies on a larger population or a longer follow-up duration are necessary to verify the current study results.

We could not identify the reason for the different AF recurrence rate seen with different energy sources. Documentation of online electrophysiologic evaluation during microwave ablation may have given an indication of the device to create transmural lesions acutely.

In conclusion, both the MW and Cryo groups show excellent early operative results, although the aortic clamping time is longer in the Cryo group compared with the MW group. Rates of atrial contractility restoration after surgery are similar in the two groups. However, patients who underwent microwave ablation exhibit tendency toward more frequent AF recurrence than those who underwent cryoablation. We assume the differences in long-term rhythm outcomes between these two energy sources are due to the difference in the ability to produce transmural necrosis. Further investigations involving histologic evaluations are needed to address this issue.

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