Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial


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Abstract

Objective: Radiofrequency or the use of microwave energy in combination with atrial size reduction during open heart surgery have been reported to be effective in up to 75% in the treatment of permanent atrial fibrillation. However, no data from prospective randomized trials using microwave energy are available. Methods: Forty-three patients with permanent atrial fibrillation undergoing open-heart surgery were randomly stratified into treatment group receiving microwave ablation and atrial size reduction (n = 24) or control group (n = 19). Patients in either group were treated with amiodarone or sotalol for 3 months if sinus rhythm or any atrioventricular rhythm was successfully restored. Follow-up time points were at 3, 6 and 12 month after surgery. Results: In the treatment group 22 out of 24 patients (91.7%) were successfully converted to sinus rhythm by using intraoperative microwave ablation therapy whereas only six out of 19 (31.5%) patients converted to sinus rhythm directly after surgery. At 12-month follow-up there were still a significantly higher percentage of patients in the treatment group free from atrial fibrillation when compared to control (80 vs. 33.3%, P = 0.036). Conclusion: The preliminary data from this first prospectively randomized trial indicate that microwave ablation combined with atrial size reduction is a safe and highly efficient treatment in permanent atrial fibrillation.

Keywords: Microwave ablation; Cardiac surgery; Atrial fibrillation

1. Introduction

Atrial fibrillation (AF) contributes significantly to morbidity and mortality particularly in elderly patients. It is a diverse arrhythmia, which is clinically divided into three subtypes; paroxysmal refers to spontaneously terminating episodes; if AF is sustained it is designated persistent; permanent AF refers to patients in which sinus rhythm (SR) cannot be sustained after cardioversion or when the patient and physician have decided to allow AF to continue without further efforts to restore SR [1]. In patients with permanent AF, therapeutical options are usually limited to rate control therapy only. Therefore different surgical methods have been developed over the last decade to restore sinus rhythm in patients with permanent AF.

Surgical ablation methods for atrial fibrillation are particularly suited to the substantial proportion of patients who have this arrhythmia concomitant with heart disease requiring surgical intervention. It is suggested that 50–70% [2] of patients undergoing valve repair or replacement and at least 2–3% of patients receiving coronary artery bypass grafting (CABG) [3] have atrial fibrillation. The Maze procedure, originally developed to address this population, has been demonstrated to be effective to eliminate AF in up to 90% [4]. However, because of its complexity and association with high postoperative morbidity [5], surgeons are reluctant to use it routinely.

Use of energy sources, such as radiofrequency, microwave, or cryoablation, as alternatives to the Maze procedure are being applied. With energy ablation, a set of transmural lesions is created in the atria where the goal of blocking
aberrant reentrant circuits responsible for atrial fibrillation is the same as the original Maze procedure. Energy ablation is technically easier to perform, is demonstrating good success rates and is associated with less risk of peri- and post-operative complications [3,6–8]. Microwave energy offers several potential advantages over other modes used for surgical ablation. Most notably, these include the ability to rapidly produce linear and deep lesions when desired, with minimal ablation. Most notably, these include the ability to rapidly produce linear and deep lesions when desired, with minimal risk of tissue surface charring or coagulation [9].

The purpose of this study was to evaluate the efficacy of surgical applied microwave energy ablation in patients with chronic permanent AF in a prospectively randomized open labeled clinical trial.

2. Materials and methods

2.1. Patient population

A total of 43 patients with permanent AF, who had been unsuccessfully treated previously, presented to our clinic for surgical treatment of valve disease and/or required coronary artery bypass grafting. Patients were randomly stratified into a treatment (n = 24) or control group (n = 19). The randomization was done according to the diagnosis of permanent atrial fibrillation regardless of the concomitant cardiac disease, since previous studies did not reveal different success rates in restoration of sinus rhythm in relation to the specific underlying cardiac disease [1,3,15]. All operations were performed between February 2001 and September, 2002 at our center.

There were 26 men and 17 women, with a mean age of 67 ± 9.4 years. The average duration of chronic permanent AF at the time of inclusion into the study was 6.2 ± 6.9 years. Data for age, gender, duration of AF, preoperative ejection fraction and left atrial dimensions are summarized in Table 1.

2.2. Microwave ablation system

The microwave ablation system (AFx Inc., Fremont, CA) consisted of a surgical ablation probe (FLEX 2) connected by a coaxial cable to a microwave generator. The ablation element was a 25-mm long antenna located at the distal end of the probe. The microwave generator delivers a continuous energy flow (2.45 GHz) and allows for variable power output ranging between 35 and 75 W, adjustable by 5-W increments. The temperature of the device was recorded through an embedded thermocouple, and the ablation element was cooled down after 5–6 ablations to keep the temperature below 40 °C to prevent overheating and uncontrolled tissue damage.

### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Microwave</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>19</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/12</td>
<td>14/5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.57 ± 10.03</td>
<td>70.21 ± 7.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(45–81)</td>
<td>(54–82)</td>
<td></td>
</tr>
<tr>
<td>Perm. AF before surgery (%)</td>
<td>24 (100)</td>
<td>19 (100)</td>
<td></td>
</tr>
<tr>
<td>(Range)</td>
<td>(0.08–8.25)</td>
<td>(0.08–24)</td>
<td></td>
</tr>
<tr>
<td>Duration of perm. AF (years)</td>
<td>3.8 ± 2.84</td>
<td>9.21 ± 9.24</td>
<td>0.05</td>
</tr>
<tr>
<td>(Range)</td>
<td>(0.08–8.25)</td>
<td>(0.08–24)</td>
<td></td>
</tr>
<tr>
<td>Perm. AF &gt; 3 months</td>
<td>88.8%</td>
<td>87.5%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62.8 ± 13.2</td>
<td>54.37 ± 17.08</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(20–79)</td>
<td>(28–88)</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>54.9 ± 11</td>
<td>53.9 ± 18.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(43–105)</td>
<td>(35–95)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. Values in parentheses denote upper and lower limit. Perm. AF, permanent atrial fibrillation; n.s., not significant.

2.3. Ablation procedure

All patients (ablation and control group) underwent valve and/or coronary artery bypass grafting (CABG) surgery with arrested heart under cardiopulmonary bypass using a standard procedure with median sternotomy. In patients who received surgical ablation, the lesion set was performed immediately prior to the valve or CABG procedure, after arresting the heart and placing the patient on cardiopulmonary bypass (CPB). Microwave energy power setting used to produce each lesion was 40 W, with ablation time of 25 s. This setup has been demonstrated to provide sufficient energy for a consistent 3–5 mm lesion depth, sufficient for transmural ablation of the myocardium [10].

After incision of the left atrium, size reduction was achieved by oversewing the orifice of the left atrial appendage. The application started at the mural mitral annulus (P2), continuous lines between the orifices ending at the mural annulus connecting completed circles within the lung veins. Finally the excluded auricle was surrounded by another continuous ablation line starting from the left upper pulmonary vein. The number of applications ranged from 17 to 38 times at 40 W (25 s each) (Fig. 1).

2.4. Perioperative protocol

Patient medication was maintained until the day of surgery except anticoagulation therapy, which was either discontinued 4 days prior to surgery or if necessary switched to heparin (i.v. or s.c.).

Left atrial dimensions were measured directly by transthoracic or transesophageal echocardiogram prior to the operation. All patients underwent a final attempt for direct electrical cardioversion (2 × 20 J) immediately before cannulation. All patients included in the study did not convert hereby to sinus rhythm. Patients were set on CPB and...
the left atrium was incised (ablation group). Microwave ablation and exclusion of the left atrial appendage was performed as previously described. Thereafter the surgical procedure (CABG and/or valve) was carried out.

2.5. Postoperative protocol

Patients were treated with either amiodaron or sotalol as antiarrhythmic medication if sinus rhythm was successfully restored and no contraindications were given. Cardiac rhythm was continuously monitored until discharge from the intensive care unit. During further hospital stay subsequent ECG tests were performed and a 24-h Holter-ECG monitoring was carried out prior to discharge. All patients were kept on phenprocoumon for a minimum of 3 months.

Follow-up time points were at 3, 6 and 12 months after surgery and consisted of repeated ECG test and a 24-h Holter-ECG at 12-month follow-up, physical examination and a 15-min interview. This was either carried out by general physicians or at our outpatient clinic.

2.6. Statistical analysis

Data are presented as mean ± SD. Parameters were distributed normally. Student’s t-tests for unpaired variables and chi-square tests were used to compare baseline characteristics. Dichotomous variables were analyzed by chi-square and Fischer’s exact test. P < 0.05 was considered statistically significant.

3. Results

A total of 43 patients were enrolled in the study after the diagnosis of permanent AF was confirmed by a final intraoperative unsuccessful attempt of electrical cardioversion. Demographic information and clinical parameters for the microwave ablation and control groups are presented in Tables 1 and 2. Two in-hospital deaths occurred. One patient (ablation group) died at postoperative day (POD) 19 due to cerebral air embolism of unknown origin. A thorough autopsy did not reveal any link to the previously performed microwave ablation therapy. The ablation lines within the left atrium and the pulmonary veins did not present any signs of excessive scar formation or rupture. The integrity of the epicardial surface along the ablation lines was not altered and there was no atroioesophageal fistula detectable. The second patient (control) died because of refractory heart failure.

In the treatment group 22 out of 24 patients (91.7%) were successfully converted to SR by using intraoperative microwave ablation therapy, however nine patients experienced a relapse and were discharged with atrial fibrillation. During further follow-up four out of these nine (44%) converted spontaneously (\( n = 1 \)) or by means of pharmacological (\( n = 1 \)) or electrical (\( n = 2 \)) cardioversion to SR. They were found to be free of AF at 12-month follow-up.

In the control group conversion rate to SR was significantly lower. Six out of 19 (31.5%) patients converted to SR directly after surgery, but only three (15.8%) were discharged in stable SR. There were no conversions to SR or any atrioventricular (AV)-rhythm achieved during further follow-up. At 12-month follow-up 80.0% of patients in the treatment group were free from AF whereas only 33.3% of patients in the time-control group experienced freedom from AF (\( P = 0.036 \)) (Fig. 2). Subanalysis with regard to underlying cardiac disease did not reveal significant differences of success rate within both groups.

Table 2
Clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>Microwave</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>3</td>
<td>5</td>
<td>n.s.</td>
</tr>
<tr>
<td>MVR (single or combined)</td>
<td>16</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>244.73 ± 63.13</td>
<td>228.95 ± 62.44</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(125–360)</td>
<td>(145–340)</td>
<td></td>
</tr>
<tr>
<td>CPB (min)</td>
<td>120.59 ± 27.27</td>
<td>103.79 ± 45.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(78–176)</td>
<td>(47–195)</td>
<td></td>
</tr>
<tr>
<td>Cross-clamp (min)</td>
<td>99.59 ± 24.79</td>
<td>74 ± 44.32</td>
<td>0.03</td>
</tr>
<tr>
<td>(Range)</td>
<td>(26–155)</td>
<td>(31–146)</td>
<td></td>
</tr>
<tr>
<td>Exclusion of LAA</td>
<td>24</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of ablation (min)</td>
<td>11.3 ± 2.3</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>No. of applications</td>
<td>27.14 ± 5.6</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>In-hospital stay (days)</td>
<td>21.5 ± 13.26</td>
<td>20 ± 11.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>(Range)</td>
<td>(9–52)</td>
<td>(12–57)</td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>1 (4.2)</td>
<td>1 (5.3)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. Values in parentheses denote upper and lower limit. CABG, coronary artery bypass grafting; MVR, mitral valve repair replacement; CPB, cardiopulmonary bypass; LAA, left atrial appendage; n.a., not available.
During the follow-up period none of the patients presented with signs of pulmonary vein stenosis. In addition, in those patients receiving echocardiography, there was no evidence for changes in pulmonary vein anatomy noted.

Adjuvant antiarrhythmic therapy was applied only when either SR was restored post surgery or a clinical significant tachyarrhythmia occurred and no contraindications were given. A total of 29 patients (20 treatment vs. nine control) were treated with amiodaron \((n = 25)\) or sotalol \((n = 4)\). 86.2% of those \((85\% \text{ treatment vs. } 100\% \text{ control})\) completed a 3-month course. Antiarrhythmic therapy was discontinued in five patients due to new onset of bradycardia \((n = 3)\), drug-related side effects \((n = 1)\) or no compliance \((n = 1)\). All three patients with new onset of bradycardia required implantation of a pacemaker because of sinus arrest \((n = 1)\) or atrioventricular dissociation \((n = 2)\). With respect to freedom from AF at 12-month follow-up there was no difference observed among patients treated with or without antiarrhythmic drugs (Fig. 3).

### 4. Discussion

Currently, there are several modes of treatment used against permanent AF; however, these therapies are not curative and serve principally to ameliorate symptoms. Because AF is allowed to continue, traditional palliative measures are not likely to reduce the risk of stroke or early mortality associated with AF. In addition, pharmaceutical therapy is not effective in approximately 50% of cases and has even been observed to induce intolerable, or even life-threatening side effects [11–13]. In response to these limitations, surgical procedures, which directly target the atrial substrate in order to eliminate atrial fibrillation and restore normal atrial function, are of particular interest.

The Cox Maze procedure has been shown to be highly efficient; however, due to the complexity of the method it is technically very demanding and time consuming. Furthermore, the association with a considerable postoperative mortality and morbidity rate has not rendered a widespread application.

The use of energy sources to create transmural lesions has facilitated the Maze procedure. Various modifications using radiofrequency, cryoablation and microwave energy with or without additional atrial size reduction have been described.

The specific advantages of microwave energy over other modes of energy application principally are a result of the unique way in which it heats tissue. The electromagnetic field introduced into the tissue induces bipolar molecules, particularly water, to vibrate and rotate, resulting in increased frictional heating. The tissue temperature hereby does not exceed 40°C, helping to keep the integrity of the myocardium and thereby preventing life-threatening complications. The formation of atrio-esophageal fistulas, which has been described, with the use of radiofrequency has been suggested to be caused by excessive overheating of myocardial tissue with temperatures measured on the epicardial surface of 60°C [14].

The reported mid- and long-term success rates in preventing recurrence of AF vary between 69 and 75% [3,8,14,15]. However, a careful evaluation of these promising results in a randomized controlled study is not available.

In this first prospectively randomized trial using microwave energy we were able to demonstrate an initial success rate of 91.7% that was significantly higher when compared to 47.4% of time-control. Although this success rate dropped to 60.8% during hospital stay, we found 80.0% of patients in the treatment group to be free from AF at 12-month follow-up. This might be in part due to the complex remodeling processes that are initiated through the re-establishment of SR or any AV-rhythm. In this regard Hobbs and coworkers [16] have described the reversibility of atrial electrical remodeling in patients with persistent atrial fibrillation. It has been suggested that during a ‘remodeling reversal phase’ the atria are in a state of increased vulnerability, which renders an increased risk of recurrence of AF [17]. We propose that under the condition of a previously performed left atrial ablation this ‘period of instability’ in which multiple switches from SR to AF and vice versa occur, will turn into a ‘period of stability’ where...
the blockage of reentrant currents will maintain a status of freedom from AF.

Interestingly, we could not find an additional effect of antiarrhythmic therapy with amiodaron or sotalol in stabilizing SR or any AV-rhythm at 12-month follow-up. This is somewhat surprising since in particular amiodaron has been shown to be highly efficient in preventing recurrence of AF in patients with paroxysmal or persistent atrial fibrillation. However, little is known about the efficacy of amiodaron in the treatment of permanent AF. Fragakis and coworkers [18] have described a poor efficacy of antiarrhythmic therapy including amiodaron in the prevention of recurrence of AF in patients with permanent atrial fibrillation. Nonetheless, all these findings have to be treated with caution since the number of patients investigated is small and needs to be addressed in a larger collective.

The ablation lines performed in our study aimed to eliminate anatomically determined left atria 'anchor' reentrant circuits [19] and to isolate ectopic beats originating in the pulmonary veins [20]. We did not use a biatrial ablation approach although the possibility of recurrence of AF due to foci originating from the right atrium has been recognized [21]. However, the expected incidence of recurrence of AF due to foci from the right atrium is approximately 10–14% [20,22]. Considering the relatively small number of patients who would benefit from a both-sided microwave ablation, restriction to the left atrium appears to be appropriate, particularly since good success rates of catheter-based ablation techniques in patients with AF originating from the right atrium have been reported [15,23]. In our treatment group there were two patients who where successfully converted to SR and AV-rhythm by means of radiofrequency catheter ablation 5 and 15 months after microwave ablation.

There have been severe adverse events described with the intraoperative use of radiofrequency ablation technique, in particular the occurrence of atrioesophageal fistulas with consecutive cerebral air embolism. Although the mechanism leading to the described esophageal injury has not been clearly elucidated, a thermal injury in combination with mechanical alteration of the esophagus due to the concomitant use of a transesophageal echocardiography probe has been proposed as the most likely cause. In our series one patient experienced a sudden stroke at POD 16. He was immediately transferred to the intensive care unit because of respiratory failure and put on ventilation. Repeated CT scans revealed massive disseminated cerebral air embolism with increasing cerebral edema. The patient died 3 days later. The subsequent autopsy specifically excluded any link to the previously performed microwave ablation therapy as described above, and the source of air embolism remained unknown. There were also no signs of upper gastrointestinal bleeding pre- and postmortem. Until now approximately 1500 microwave procedures have been carried out worldwide and no procedure-related complications have been reported so far.

We conclude that the subendocardial microwave ablation technique is safe and highly effective in patients with permanent atrial fibrillation for whom rate control therapy would be the only therapeutical option. Restoration of SR or any AV-rhythm has been previously demonstrated to improve left atrial transporter function [24] and has been recognized as an independent factor to prevent late stroke [25]. Thus larger trials to investigate the long-term outcome with regard to quality of life and stroke prevention are warranted.

References


Appendix A. Conference discussion

Dr A. Parolari (Milan, Italy): My questions are: first, if you could explain what was your randomization method. Second question: how can you explain the massive air embolism on the 17th postoperative day?

Dr Schuetz: I would like to give the question to the audience. Do you have an explanation for the fact that the air embolism started on the 17th day after operation. We could not explain this phenomenon; in particular our pathologists did not see any contact between esophagus, pulmonary veins, atrium, and atrial connections.

Dr Parolari: Were there any pericardial lesions between the left atrium and pericardium or was it all free?

Dr Schuetz: There were no lesions. The statistical analysis of our results were tested by our Department of Statistics. In addition, we have an ongoing study in the initial phase and the data presented today are our preliminary data.

Dr K. Khargi (Bochum, Germany): I would like to have your thoughts on why you didn’t observe any atrial flutter in your series. You would expect some incidence if you are only doing a left atrial lesion pattern. Normally speaking, you would expect 5–10% or 5–8% atrial flutter. Is there something special in your technique which avoids that?

Dr Schuetz: As I mentioned during the presentation, I reported three atypical atrial flutters, which were treated by our cardiologists after operation, and now these three patients are in a regular sinus rhythm. But there were three patients with atrial flutter.

Dr P. Mohr (Leipzig, Germany): I would just like to make a comment about the air embolism, because the history you were mentioning is something which is occurring in several centers worldwide for patients 1 week after A-fib surgery, being recognized as a stroke sometimes after breakfast. We had an experience in four patients: two patients had a clear perforation, two patients did not have a perforation but they had neurological symptoms, like after breakfast after 1 week, and with the CT scan we did see some air in between the left atrium and the esophagus. We were alarmed from the previous cases and finally we found out, despite the fact there was no open connection, that there was thermal injury to the esophagus; the patients had an esophageal resection afterwards, and then the study revealed there was some thermal injury. I think it is quite possible, especially if you ablate around the left or right, depending on the location of the esophagus, if you use endocardial monopolar thermal injury, that you can injure the esophagus as well, and through high pressure, through swallowing, those patients may have migration of air, and that may cause that kind of neurological damage. And I think that merely a gross microscopy doesn’t say anything. The CT scan is a perfect hint to find that out.

Dr Schuetz: Anyway, do you believe that it can occur after 17 days, is it possible?

Dr Mohr: The cases we had all occurred after 1 week to 10 days. They had been admitted to the rehab after 14 days. I am pretty sure it can occur. It just depends on the patient. Maybe these are the patients who have esophagitis or reflux, or something like that. What is clear from the animal experiments we are doing now is this: you can take radiofrequency of the esophagus or you can also take microwave; even if you freeze it and you press down you will have an injury to the neighboring organs, which we haven’t reflected on, any of us, when we started that, and I think that is a major concern. The only way to avoid that right now is if you use radiofrequency, I think bipolar, and if you use cryo, you can pull the wall up to avoid contact to the posterior wall. But everything else needs to at least be considered, and a stroke symptom after 1 week for me is a severe hint that something like that could have occurred.
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