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Epicardial microwave ablation of permanent atrial fibrillation during a coronary bypass and/or aortic valve operation: prospective, randomised, controlled, mono centre study (EPIMIK)

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Abstract

Atrial fibrillation (AF), one of the most common arrhythmias, is the aetiology behind a high percentage of strokes. Recently simplified ablation procedures became more relevant in the surgical treatment of AF. One advantage of microwave ablation (MW) is that it can be used epicardially. We report our results of a prospective, randomized, controlled, mono centre trail. In two arms, with and without ablation, we treated patients with documented permanent atrial fibrillation with an indication for cardiac surgery, where opening of the left atrium was not required.

Methods: Patients, who were scheduled for aortic valve replacement and/or coronary artery bypass grafting suffering from permanent AF, were included in the registry. After inclusion the patients were randomized either to epicardial MW (EMW) as a concomitant procedure during their operation (Group A) or equivalent operations without ablation therapy (group B). Follow-up was one year. EMW was performed under extracorporeal circulation on the beating heart creating a box lesion including the anterior part of the pulmonary veins with connection lines on the roof and bottom of the left atrium and an additional line to the left atrial appendage.

Results: 45 Patients (17 female/28 male) with AVD and/or CAD and pAF were included. Preoperative duration of pAF was 5.2 years (0.1-45 years). Preoperative data were as follows: mean age: 74 years (63-83 years), mean ejection fraction: 56% (30–83%), left atrial diameter: 46.1mm (40-59mm). 20 patients got aortic valve replacement, 17 had CABG, and 8 operations were combined procedures (AVR and CABG).

All ablation procedures were performed on-pump beating heart. We observed no device related complications. During the follow-up, restoration of the sinus rhythm rate after one year is 52.4% in the ablated patients in contrast to 10.5% in the control group. The 30-day survival rate in group A was 87.5% and 95.2% in group B (n.s.). Pacemaker implants after one year were required in 12.5% in group A and 25% in group B.

Time po.	10 days	30 days	90 days	180 days	360 days
SR in group A (%)	43.50	22.72	25.00	50.00	52.4
SR in group B (%)	0.0	9.52	10.53	15.00	10.0

Conclusion: Our results demonstrate that EMW is an effective treatment option for patients with permanent AF. The procedure is less invasive than the endocardial approach and prolongs concomitant heart surgery only minimally without lengthening of the ischemic time. We think, that EMW ablation is a promising concept with a good benefit/risk ratio for the treatment of pAF, especially in patients where opening of the left atrium is not required as part of the original procedure. A more extended lesion line concept, closer to the classic Maze procedure lines is suggested to achieve higher success rates.

EMW has become part of our daily routine for the treatment of AF in patients scheduled for bypass grafting and/ or aortic valve replacement.

Key words: prospective randomised trial, epicardial ablation, microwave energy, coronary artery bypass grafting, aortic valve replacement and permanent atrial fibrillation

Introduction

Atrial fibrillation represents with 60% the majority of all treatment dependent arrhythmias. Up to 1.5% of the general population of industrialised countries is affected. The incidence correlates positively with age, reaching 4% in individuals over 60 years of age, 7% in those over 70 and remarkable 17% of those over 84 years of age [Ezekowitz, 2003]. In the group of patients requiring mitral valve operations the incidence of atrial fibrillation is reaching up to 60 – 80% [Feinberg, Kannel, 1982]. In patients requiring surgery due to coronary artery disease the incidence was estimated to be approximately 5 to 10%. [Quader, 2004]. AF doubles mortality and increases dramatically the risk and severity of stroke. A patient with AF and a prior cerebral ischemia has a risk of 10-12% per year to suffer from a stroke [Ryder, 1999]. Medical treatment aimed at either rhythm or rate control does not yield satisfactory results [Deisenhöfer, 2012; Andresen & Trappe, 2012]. Therefore different surgical methods have been developed over the last decade to restore sinus rhythm in patients with permanent AF. The Maze method, although recognized as the therapeutic gold standard, remains due to its complexity a procedure rarely undertaken. The creation of the recently established ablation techniques utilising different forms of energy, was adjusted to the concept of the Cox-Maze procedure and predominately used endocardially. Mitral valve surgery is favourable for the implementation of this kind of technique because the incision of the left atrium is already required as part of the surgical procedure. This is different to operations (like coronary artery bypass grafting or aortic valve replacement), where opening of the left atrium is not required. Otherwise, it is conducted in those operations where no primary atrium incision is required.

In those cases, in order to apply ablation, it was necessary to additionally conduct an atrial incision (with additional bicaval cannulation and prolonged cross clamping time). In order to simplify the ablation procedure the epicardial ablation was introduced. [Maessen, 2002, Mazzitelli, 2002]. At first we ascertained the feasibility and safety of epicardial microwave ablation in a pilot study. The second step was to evaluate the clinical effectiveness of the therapy. The best way to realize this is a prospective, randomised, controlled trial. Therefore we created a study design, where patients who were referred to our institution for an aortic valve and/or coronary bypass operation and suffered from permanent atrial fibrillation were randomly assigned to epicardial ablation therapy or no ablation therapy. The latter served as control group. We now present the results of this first randomized trial worldwide.

Materials and Methods

The examination was carried out in a monocentric, prospective, controlled and randomised manner. The inclusion criteria consisted of an existing indication to coronary bypass and/or aortic valve surgery with additional permanent atrial fibrillation ($\geq$ 1 month), a left ventricular ejection fraction of $\geq$ 30% and an age of $\geq$ 18 years.
Exclusion criteria were as follows:
- emergency operations,
- age $<$ 18 years,
- left ventricular ejection fraction $<$ 30%,
- stroke in the past 3 months,

- myocardial infarction in the last 30 days,
- previous heart operations,
- necessary left atrium incision during the surgery,
- necessary right atrium incision during the surgery,
- acute myocarditis,
- existence of a thrombus in left atrial appendage,
- heart failure NYHA IV,
- implanted pacemaker,
- implanted defibrillator,
- pregnancy and breast feeding,
- known drug dependency,
- legal/social incapacity and/or other situations which do not allow the patient to fully understand the essence, meaning and consequences of this study.

Primary endpoint of the study was the incidence of sinus rhythm after 30, 90, 180 and 360 days postoperatively. The occurrence of atrial fibrillation or atrial flutter was judged as treatment failure. The number of the participants required (n = 45) was determined with the help of a sample size calculation based on the results obtained in a pilot study. The benefits and risks of the ablation treatment and the randomized design of the study were thoroughly explained to all patients before the operation. They all signed an informed consent form and a declaration form allowing usage of personal data for medical research purposes. All patients who met the inclusion criteria and none of the exclusion criteria were included in the project. The study was approved by the ethical committee of the Carl Gustav Carus medical faculty of the Technical University of Dresden (EK2012005).

After the patients gave informed consent, they were randomly assigned to the therapy group (epicardial microwave ablation (EMW)) or the control group (equivalent operation without EMW)

Patients

A total of 45 patients with permanent AF was included, who were admitted to our clinic for surgical treatment of aortic valve disease and/or coronary artery disease.

Preoperative data like gender, age, duration of AF, ejection fraction and diameter of the left atrium (transthoracic view) are presented in table 1.

Cardiovascular risk factors and concomitant diseases are summarized in table 2.

Table 3 lists all conducted heart operations. In all heart valve replacement procedures, biological prosthetic valves were implanted.

There was no significant difference of demographic, clinical and surgical values (with the exception of the preoperative duration of

	Microwave n=24	**control n=21**	**p**
Sex (m / f)	14 / 10	14 / 7	0.5651
Age (years)	74 ± 4.4	74.8 ± 5.8	0.57
Range (years)	63 – 79	65 – 85	
AF before surgery (years)	5.9 ± 4.4	4.3 ± 8.0	0.035
Range (years)	0.1 – 45	0.1 – 11.0	
Ejection fraction (%)	55.8 ± 13.6	54.2 ± 5.5	0.1853
Range (years)	30 – 77	35 – 83	
Echocardiography			
Left atrial diameter (mm)	45.1 ± 4.1	47.3 ± 5.5	0.350
Range (mm)	40 – 53	40 – 59	

Table 1: Patient characteristics in both groups.

Table 2: Cardiovascular risk factors and diseases of both groups.

	Microwave n=24	control n=21	p
Arterial hypertension	83.3%	90.5%	0.361
Pulmonary hypertension	25.0%	19.0%	0.632
Diabetes mellitus	66.6%	47.6%	0.197
Hyperlipidemia	70.8%	80.9%	0.431
Smoker	8.3%	19.0%	0.292
Body mass index	28.8 ± 2.8	28.5 ± 3.9	0.260
Coronary artery disease	83.3%	71.4%	0.338
Prior myocardial infarction	12.5%	28.6%	0.179
Prior stroke	4.1%	4.7%	0.923
Renal insufficiency Stage 2 or 3	41.6%	42.6%	0.30

Table 3: Conducted heart operations.

	Microwave n=24	control n=21	p
Isolated coronary revascularization	10	7	0.565
Isolated aortic valve replacement	11	9	0.841
Combination procedure	3	5	0.322
Duration of operation (min)	172.6	150.2	0.0026

the AF and the length of the operation) between the two groups. Hence, there is homogeneity of initial patient status and a comparison of results between the two different treatment groups can therefore be made.

Microwave ablation system

The Guidant Corp. (Santa Clara, CA, USA) microwave surgical ablation device (FLEX4®) was used to produce linear lesions on the epicardial surface. Details of the method were previously described [Knaut, 2004]. The FLex4® was used with energy of 65 W for 90 s for each ablation step, in an overlapping technique.

Ablation procedure

The epicardial ablation was carried out in a rather simplified manner, schematically depicted in Figure 1. The pericardial folds at the vena cava inferior and vena cava superior were dissected. Extended fat tissue in the interatrial groove and the left atrial roof was partly removed. We consciously selected a rather simplified lesion line concept including only the anterior part of the pulmonary veins and connecting lines at the left atrial roof and bottom in order to minimize the surgical effort by preparing the posterior part of the pulmonary veins. Nevertheless we held on to the ablation line to the left atrial appendage. Due to the close proximity of the circumflex arteries no lesion in direction to the mitral valve was made.

Perioperative protocol

The preoperative medication was regularly administered until the day of the surgery (including thrombocyte aggregation inhibitors like Aspirin and Clopidogrel). In the few cas-

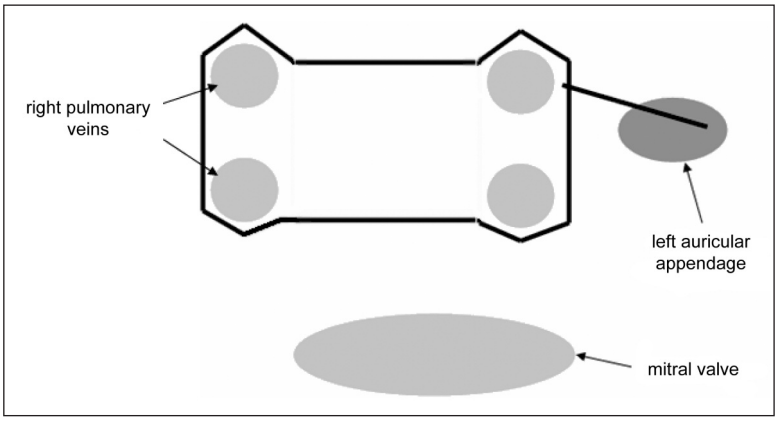

Figure 1: Diagram of the epicardial lesion performed in the group treated with ablation therapy.

es of long term vitamin K antagonist therapy, medication was changed to low molecular weight heparin in advance.

Left atrial dimensions were measured directly by transthoracic or transesophageal echocardiogram prior to the operation. Additionally, we excluded a thrombus formation in the left atrial appendage. In case of randomization to ablation therapy the patient was put on cardiopulmonary bypass. The operation started with the ablation procedure performed on the beating heart. Afterwards the aorta was crossclamped and the operation continued in the routine surgical manner.

Postoperational control

From the first postoperative day and continued for at least 6 months, the patients received a conventional ß-blocker (normally Metoprolol) in order to stabilise the restored sinus rhythm and oral anticoagulation with Phenprocoumon targeting an INR between 2.0 and 2.5. The postoperative heart rhythm was controlled daily until the tenth postoperative day. Follow up examinations were carried out on days 30, 90, 180 and 360 postoperatively. The rhythm was evaluated with a 12-channel ECG and 24h Holter ECG on 180. and 360. postoperative day. A regular transport function of both atria was defined by the existence of an A- and E- in the transthoracic echocardiography. In cases of recurring AF (until the 90. postoperative day), we performed up to 2 cardioversions.

Statistical analysis

For the calculation of the case number there was a $2\alpha = 0.05$, $\beta = 0.10$ with a $p1 = 0.15$ and $p2 = 0.65$ adopted.

Continuous data are presented as mean value $\pm$ standard deviation; classified data with percentage frequency. The student´s t-test two-tailed for independent samples or the Chi square test was used for group comparison. Probability values less than 0.05 were interpreted to indicate a statistically significant difference between the groups.

Results

One year after the procedure, sinus rhythm was restored in 11 from the 21 patients treated with ablation, (52.4%), and 2 of the 20 control patients (10%). There was therefore a significant difference in achieving one primary endpoint – incidence of SR after the operation – between the two groups ($p = 0.0099$).

In respect to chronological progression, there was again a considerable difference between the 2 groups (Log rank (Mantel Cox) test: $p = 0.0415$). A stable sinus rhythm (sinus

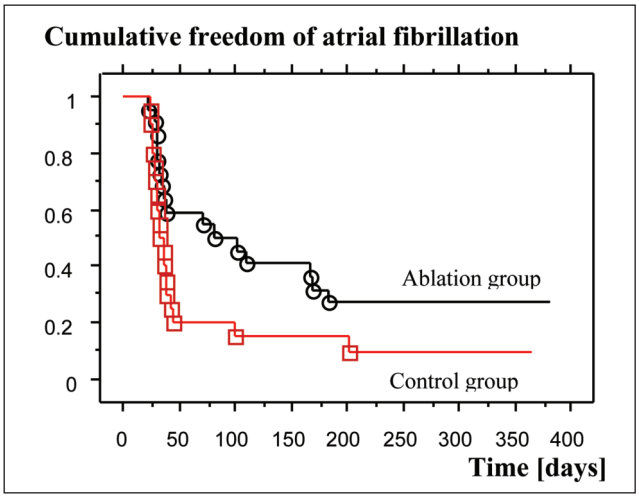

Figure 2: Cumulative absence of AF for both groups within a treatment time frame of one year (Kaplan-Meyer-Plot).

rhythm at all times of the examination) was established in 5 patients of the ablation group and in 2 of the control group. The absence of AF for both groups is shown in Figure 2.

The frequency of sinus rhythm/AF, mortality, failure rate, cardioversions and pacemaker implantation for both patient groups is shown in Table 4.

The drop out rate at the end of the study was zero. All patients could be followed until the end of the study.

In the ablation group, 3 patients died during the first postoperatively year because of the following reasons: ventricular fibrillation, left heart failure 10 days after operation and one of unknown aetiology after 12 months. In the control group 1 patient died in a septic shock (p = 0. 33). 4 patients of the control group (DDD: 2; VVI: 2) and 2 patients of the microwave ablation group (DDD: 1; VVI: 1) underwent pacemaker implantation during the first postoperative year. In the ablation group, we observed no device- or procedure-related complications.

Table 4: Sinus rhythm, mortality, failure rate, cardioversions and pacemaker implantation for both study groups over the period of one year.

Postoperative day:	**30**	**90**	**180**	**360**
	A / K	**A / K**	**A / K**	**A / K**
	22 / 21	**20 / 19**	**22 / 20**	**21 / 20**
SR - absolute - percentage	 5 / 2 22.7 / 9.5	 5 / 2 25.0 / 10.5	 11 / 2 50.0 / 10.0	 11 / 2 52.4 / 10.0
AF	15 / 18	15 / 17	11 / 17	10 / 17
Deceased	2 / 0	0 / 1	0 / 0	1 / 0
Absent	2 / 1	2 / 1	0 / 0	0 / 0
Cardioversion	7 / 1	7 / 0	13 / 1	12 / 1
Pacemaker	0 / 0	1 / 1	1 / 2	2 / 4

Discussion

In this first prospective, randomized, clinical study using microwave energy for the epicardial ablation of permanent AF during cardiac surgery (aortic valve replacement or coronary revascularization) with a simplified lesion line concept we were able to demonstrate that the rate of sinus rhythm was significantly higher with ablation compared to a control group without ablation ($p = 0.0099$). One year after the surgical intervention, 11 of the 21 surviving patients of the ablation group (52.4%) and 2 of the 20 control patients (10%), had regained and retained sinus rhythm.

The rate of spontaneous cardioversion was in accordance to the results of earlier studies (see Table 5).

The obtained success rate of 52.4% in this study, generated with a considerably simplified lesion line concept, in patients with permanent AF during a cardiovascular bypass- or/and aortic valve operation is noticeably lower than that of 65.7% (one year after the operation) achieved with a more complex surgical concept of separate ablation of both pairs of lung veins, a connection line and a line to the left cardiac auricle [Knaut, 2009]. Therefore, a complete circular ablation line around the pulmonary veins including the posterior wall seems to be of significant importance. In consequence the return to this more elaborated concept seems to be justified despite the slightly longer preparation- and ablation time of about 10 minutes.

Table 5: Spontaneous recovery of sinus rhythm on patients with permanent AF after cardiac surgery procedures without ablation (no differentiation btw. fibrillation and fluter).

First Author	Success rate	n
Handa, 1999	27.0%	39
Gaita, 2000	25.0%	18
Knaut, 2009	7.0%	287
Raine, 2004	8.5%	92
Abreu Filho, 2005	26.9%	27
Knaut, 2008	9.6%	145

Similar differences concerning the complexity of the lesion line concept were also observed during endocardial ablation procedures [Knaut-2004]. A substantial increase of the success rate from 68% to 88% in coronary bypass operations and from 78% to 85% in aortic valve operations could be achieved through a modification of the endocardial lesion line concept by implementation of Box lesions around the lung veins [Knaut, 2004, Knaut, 2006]. The generally higher success rates after endocardial ablation perhaps result form the strict resection/closure of the left atrial appandage [Cox].

In contrast to the aetiology of AF in patients with rheumatic or degenerative mitral valve disease [Boyden, 1982, Allesie, 1999], the pathomechanism of the diseases included in this study (coronary artery disease, aortic valve disease) remains largely elusive.

Limitations of the study

A limitation of this study is that the transmurality of the ablation lines was confirmed only visually. We intend to add the electrophysiological mapping to our concept in order to confirm the electrical isolation created by the ablation lines.

Furthermore, a surgically simple and fast lesion line concept was used, which can be undertaken without much training in all heart surgery procedures.

Conclusion

The current study is the first prospective controlled randomized trial involving patients with permanent AF undergoing bypass grafting and/or aortic valve replacement using epicardial ablation therapy. Sinus rhythm could be restored in 52.4% of the patients in the ablation group while this was the case in 10.0% of the patients of the control group

($p = 0.0099$).This success rate although considerably lower than that achieved through more complex lesion line concept, has yet the undeniable advantage of being able to be performed in an easier and faster manner.

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