Clinical outcomes differ among the different ablation technologies used for surgical atrial fibrillation therapy

Wyniki leczenia migotania przedsionków z zastosowaniem różnych technologii chirurgicznej ablacji

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Kardiochirurgia i Torakochirurgia Polska 2010; 7 (3): 257–264

Abstract

Multiple ablation technologies are used to provide atrial fibrillation therapy during cardiac surgery. A rigorous search was performed to identify all peer-reviewed papers that provided clinical outcomes data following the ablation therapy. A META analysis showed significant differences in clinical outcomes by ablation technology type: clinicians using temperature-controlled RF power delivery achieved higher rates of normal sinus rhythm at follow-up and patients ablated with microwave ablation had lower rates of normal sinus rhythm than the average of all ablation-treated patients. Permanent pacemaker implantation rates were higher than average for patients treated with microwave or argon-based Cryoablation technologies, but were lower than the average for patients treated using temperature-controlled RF.

Key words: cardiac surgery, ablation technology, atrial fibrillation, META analysis, COX maze.

Streszczenie

W leczeniu migotania przedsionków podczas operacji serca stosowane są liczne technologie. Dokonano skrupulatnych poszukiwań wszystkich publikacji poddanych recenzji naukowej i podających wyniki kliniczne leczenia z zastosowaniem ablacji.

Metaanaliza pokazała znaczące różnice w wynikach klinicznych w zależności od technologii ablacji: klinicyści stosujący ablację z użyciem prądu o częstotliwości radiowej (ang. *temperature-controlled RF*) uzyskiwali wyższy odsetek prawidłowego rytmu zatokowego w badaniu kontrolnym, zaś pacjenci poddani ablacji mikrofalowej wykazywali niższy odsetek prawidłowego rytmu zatokowego aniżeli średnia wszystkich pacjentów leczonych ablacją. Odsetek wszczepienia stałego rozrusznika (ang. *permanent pacemaker*) był wyższy od średniego u pacjentów leczonych technologią mikrofalową lub krioablacji z zastosowaniem argonu, a niższy u pacjentów leczonych z użyciem prądu o częstotliwości radiowej.

Słowa kluczowe: chirurgia serca, technologia ablacji, migotanie przedsionków, metaanaliza, metoda labiryntu Coxa.

Introduction

Atrial fibrillation (AF) affects about 3 million people in the United States and about 5 million people in Europe. In both regions, the yearly rate of new diagnoses of AF is about 10% of the incidence (e.g. about 300,000 for the US). Because AF has an increasing prevalence with both increasing age and with increasing severity of cardiac disease, a significant subset of AF patients have cardiac surgery each year (about 80,000 in the US, or about ¼ of the incidence of AF). Thus, over time the cardiac surgeon could significantly impact AF in Europe and in the US by treating all cardiac surgery patients with concomitant AF procedures.

When the only option for concomitant AF procedures was to add the Cox Maze cut-and-sew procedure to the primary indicated surgery, few surgeons opted to perform concomitant AF. However, with the advent of easier-to-use energy based surgical ablation devices, cardiac surgeons are adopting concomitant AF procedures in increasing numbers. As the procedure becomes more accepted, surgeons are seeking objective evidence for making decisions on which ablation technology to use and on how to apply that technology. This META analysis provides information on the clinical outcomes achieved by many investigators using different ablation technologies.

Methods

Paper identification and selection process

The CTS database was used to locate the great majority of the papers initially reviewed for possible inclusion in the

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analysis presented in this paper. We included both online and printed published papers that were accepted into publication by peer review; data from abstracts were not used. One set of searches focused on procedure type, including the following search terms: Cox Maze, AF Surgery and surgical maze. Another set of searches focused on ablation tool or procedure brand names, including COBRA, Flex, Cardioblate and CryoMaze. Other searches that successfully identified references included searches on AF-focused companies such as AtriCure, CryoCath and AFx. PUBMED searches were also employed, but those searches yielded only about 30 additional papers not found in the CTS database. Finally the references cited in the assessed papers were reviewed to identify any additional papers missed by the electronic search process. This exhaustive search yielded more than 200 references.

The META analysis includes all papers that provided clinical outcomes for ablative treatments provided by commercially available technologies that could be classified into the following groups:

Group I: RF Ablation with temperature-controlled power delivery [1-26].

Group II: Monopolar RF ablation without temperature-controlled power delivery. This group includes systems with power delivery at set voltage, current or power, and systems that shut off RF power based on system impedance [27-48].

Group III: Ablation using microwave [49-60].

Group IV: Bipolar RF ablation with clamping technology. In this group, impedance or temperature was used to modify RF power delivered to the tissue or to terminate RF power [61-78].

Group V. Cryoablation based on the extreme cooling attained by expanding argon gas [79-84].

Group VI: Ablation using High Intensity Focused Ultrasound (HIFU) [85-87].

We excluded all papers that used none of the technologies in the selected groups or that used two or more of those technologies. We also excluded all papers describing outcomes for 10 or fewer patients because of concerns about the learning curve and patient selection bias issues. This exclusion had almost no effect on the statistical power of our analyses. We also excluded several references that failed to provide data in a manner that we needed for our META analysis (e.g. if it was not possible to extract actual numbers of patients evaluated at a given time point). One reference was eliminated because another paper reported on the same patient data set (the data were consistent in the two papers). Table I shows the number of papers and patients outcomes used as input to the META analysis for each of the six technologies.

Definition of surgical ablation success

We defined percent of therapeutic success for patients that had documented AF prior to surgery as the percent of patients in normal sinus rhythm (NSR) after surgical AF therapy without any additional invasive rhythm therapy. Patients treated by an EP procedure for any atrial tachyarrhythmia (generally AF, right atrial flutters or left atrial flutters, but including focal atrial tachyarrhythmias as well) following surgery were placed in the therapy failure group at all evaluation time points following the EP procedure. Furthermore, patients treated by a second cardiac surgical procedure such as Cox III Maze following an initial surgical ablation procedure were placed in the therapy failure group at all evaluation time points following the second surgical AF procedure. Patients not treated with a device from a particular technology group because of an ablation device failure were placed in the therapeutic failure group for that technology at all evaluation time points. Patients getting pacemakers or defibrillators in the hospital following the ablation procedure or within the first 30 days of surgery were placed in the therapy failure group at all evaluation time points, unless the implant was planned prior to the ablative therapy.

There were many categories of clinical outcomes data that were not used in our definition of success. Most notable is the patient's use of antiarrhythmic drugs. The authors are well aware of the current recommendations of the Heart Rhythm Society/STS guidelines to report such data. However, few papers reported patient use of antiarrhythmic drugs in both success and failure groups. Thus, reporting on NSR rates without drugs was not feasible for this report. Right or left atrial function was not used to define ablative success even when reported.

Tab. I. The number of papers and patients used as input to the META outcomes analysis for each of the six ablation technologies

Technology	Number of publications	Number of patients	Percent paroxysmal
RF with temperature	26	1731	13%*
RF with no temperature	22	1453	24%
microwave	12	592	10%*
bipolar	18	1256	39%**
CRYO	6	331	33%**
HIFU	3	235	38%**
averages (all technologies)	87	5596	24%

** significantly lower than average; ** significantly higher than average.*

Tab. II. Percent of successful outcomes at 6 and 12 months following the index procedures achieved by each of the six technologies, including all AF types treated

Technology	6 months		1 year	
all patients	n	% NSR	n	% NSR
RF with temperature	586	80%**	709	79%**
RF with no temperature	737	69%	909	72%
microwave	494	59%*	110	55%*
bipolar	497	71%	493	72%
CRYO	211	77%	136	73%
HIFU	229	74%	84	70%
averages (all technologies)	2754	71%	2441	73%

** significantly lower than average; ** significantly better than average.*

Tab. III. Percent of successful outcomes for non-paroxysmal AF patients at 6 and 12 months following the index procedures achieved by each of the six technologies

Product	6 months		1 year	
non-paroxysmal AF patients	n	% NSR	n	% NSR
RF with temperature	361	77%**	474	76%**
RF with no temperature	553	69%	534	72%
microwave	360	54%*	110	55%*
bipolar	165	64%*	137	64%*
HIFU	136	68%	34	68%
averages (all technologies)	1633	67%	1323	71%

** significantly lower than average; ** significantly better than average.*

Tab. IV. Percent of successful outcomes for paroxysmal AF patients at 6 and 12 months following the index procedures achieved by each of five technologies

Product	6 months		1 year	
paroxysmal AF patients	n	% NSR	n	% NSR
RF with temperature	46	91%	40	93%
RF with no temperature	39	85%	51	78%
bipolar	74	80%	80	89%
HIFU	57	82%	21	76%
averages (all technologies)	216	84%	192	78%

** significantly lower than average; ** significantly better than average.*

Tab. V. Comparisons of success rates achieved in paroxysmal versus non-paroxysmal patients at 12 months achieved by four technologies

Product	Paroxysmal AF		Non-paroxysmal AF	
	n	% NSR	n	% NSR
RF with temperature	40	93%	474	76%**
RF with no temperature	51	78%	553	72%
bipolar	80	89%	137	64%*
HIFU	21	76%	34	68%
averages (all technologies)	192	78%	1213	72%

** significantly lower than average; ** significantly better than average.*

According to the new Heart Rhythm Society/STS guidelines, no person that is being considered for further AF treatment should be considered to be in permanent AF. Instead, patients that have been in AF continuously should be classified to be long-standing persistent AF patients, Thus, in the spirit of the current Heart Rhythm Society/STS guidelines for reporting treatment success, no patient was classified as irreversibly in AF (i.e. in permanent AF) if treatment continued after a detected episode of AF. Thus the outcome for a patient known to be in AF at 6 months post surgery but in continuous normal sinus rhythm at 12 months was considered a failure at 6 months but a success at 12 months.

Tab. VI. Pacemaker implantation rates for the six ablation technologies

Technology	Pacemaker implantation rate
RF with temperature	2.2%*
RF with no temperature	6.1%
microwave	17.2%**
bipolar	5.1%
CRYO	13.5%**
HIFU	6.8%
averages (all technologies)	6.6%

** significantly lower than average; ** significantly better than average.*

Evaluation of rhythm status

Because reliable preoperative assignment of patients into classes of persistent AF versus permanent AF (now classified as longstanding persistent) was not possible from the data presented in most papers, these two groups were combined and labelled as non-paroxysmal and were compared to paroxysmal AF patients.

Paroxysmal AF patients required a 24-hour Holter rhythm or its equivalent to establish that patients experiencing tachyarrhythmias following surgery were in NSR at a given evaluation time point (e.g. patients in AF at the three-month evaluation time were classified as in AF at the 6-month time point if the only evidence of 6-month NSR status was an isolated ECG strip).

Non-paroxysmal AF patients required 12-lead ECG (and free of AF symptoms) to establish that patients experiencing tachyarrhythmias following surgery were in NSR at a given evaluation time point (e.g. patients in AF at the three-month evaluation time were classified as in AF at the 6-month time point if there was no documented ECG evidence of NSR at 6 months).

Assumptions used to calculate NSR rates when data were missing from papers

Outcomes data used in the META analysis were sometimes incomplete in the papers used for the META analyses reported herein. The most common issues relate to pacemaker implant rates and its influence on patient outcomes. Most papers report an overall pacemaker implantation rate, but give no information on the number of pacemakers in the reported "AF-free" group or the "AF" group. In those cases, we assume that the pacemaker implantation rate was the same in both groups.

The number of curative EP procedures or the number of pacemaker implants following surgery is often reported without an indication of the timing of each of those procedures. In those cases, we assume that the EP procedures or pacemakers implant procedures occur early in the follow-up periods. The number of patients evaluated at each post-op milestone (e.g. 6-, 12- and 24-month follow-up) is often provided, but the rate of pacemaker implantation or EP procedure history of the actual patients included in each milestone follow-up time is not provided. In those cases, the percentage of patients treated with pacemakers or EP ablation procedures were assumed to be equal at all rhythm evaluation time points (e.g. if 4 of 50 total patients had EP ablation during the evaluation period, but timing was not defined, then we assumed that 4/50 or 8% of the 22 patients studied at one year post-op were surgical failures).

Statistical methods used

All data subjected to the META analysis are categorical data and are presented in contingency tables. Chi Squared analysis was used to determine if the patient outcomes were different among the patients treated with the six technologies. If this test indicated that the outcomes (e.g. NSR rates) were not the same, then a Fischer Exact Test was done comparing the outcomes achieved with each particular technology to the outcomes achieved with all other technologies. Since 5 or 6 such comparisons were made, only p values < 0.01 were considered significant. The results from these analyses are presented in tables.

Results

Chi Squared analysis showed that there were highly significant differences in the success rates among all AF patients treated with the six technologies. The Fischer Exact Test identified one technology with higher success rates than the average result (RF with temperature control) and one with significantly lower success rates (microwave). CRYO, HIFU, bipolar RF and monopolar RF without temperature control were not different from the averages outcome. We also redid the statistical analysis excluding microwave technology, since it is currently not commercially available. In that analysis, RF with temperature control had higher success rates than the average result, and the success rates for the other four were not different from average.

In some studies of clinical outcomes of surgical AF therapy, investigators have reported that success is higher for paroxysmal patients. Since the percent of patients in paroxysmal AF was significantly different among ablation technologies (Table I), we also completed additional META analyses on the subsets of non-paroxysmal patients and of paroxysmal patients. The microwave papers reported few separate results by AF types, so the success rates for only 5 technologies were compared for the subsets of paroxysmal and non-paroxysmal patients.

Non-paroxysmal patients treated with ablation devices using RF with temperature control had significantly better success rates than average and those treated with microwave or bipolar had lower success rates than average. For paroxysmal patients, all technologies provided statistically the same success rates. A comparison of the success rates for patients treated with all technologies shows that the reported success rates for paroxysmal patients is higher than for non-paroxysmal patients with a highly statistically significant confidence level. In addition, the success rates for all technologies were significantly better for paroxysmal AF patients than for non-paroxysmal patients.

Chi Squared analysis showed that there were significant differences in the pacemaker implantation rates among the patients treated with the six technologies. The Fischer Exact Test identified one technology with a lower pacemaker implantation rate than the average result (RF with temperature control) and two with significantly higher implantation rates (microwave and CRYO). HIFU, Bipolar RF and monopolar RF without temperature control were not different from the averages of all other technologies.

Discussion

Our META analysis showed highly statistically significant different outcomes for surgical AF therapy when different ablation technologies were used. These differences could result from differences in the patient populations studied, differences in the lesion sets that can be created by the different ablation technologies and differences in lesion-making effectiveness of the different technologies. It is quite clear from Table I that the patient population differed significantly among the sets of patients studied using the different technologies. Specifically, the percentage of paroxysmal patients treated with the different technologies differed greatly among the technologies studied. However, repeating the META analysis on the subset of patients identified as non-paroxysmal showed no changes in the technologies with higher treatment success rates or those with lower success rates than average compared to the analyses using all patients. In both cases, RF with temperature control had higher success rates and both microwave and bipolar had lower success rates than average.

It is interesting to note that for paroxysmal patients, bipolar ablation has a success rate that is not inferior to the average rate for all technologies, whereas the results are clearly inferior for chronic patients. In fact, the difference in success rates between paroxysmal and non-paroxysmal

patients was larger for this technology than for any other. One possible explanation for the better relative performance for this technology when treating paroxysmal AF patients compared to non-paroxysmal patients relates to the more limited lesion set often used with this technology, If this is the correct explanation for these results, then these results re-enforce the concept that a more complete lesion set is especially important for persistent and long-standing persistent AF patients as has been previously reported in individual series by other authors.

Our META analysis results are at least suggestive that lesion-making effectiveness varies by the type of ablation technology. Finding such technological differences is not surprising, since these technologies have been commercially introduced relatively recently. The first commercial ablation devices designed to treat AF surgically were introduced just over 10 years ago. Since then a number of differing devices have been developed to enable surgeons to treat AF surgically. To better understand why such differences among the devices may exist, it is useful to understand how these devices create lesions.

All currently available ablation devices use temperature extremes to create lesions. Most systems apply energy to the target tissue to heat it; wherever tissue temperature exceeds 50°C, myocytes are killed. If Cryo probes are used, myocytes are killed when local temperatures reach temperatures below –40°C. Whichever ablative device is used, the affected electrically responsive tissue is replaced by non-responsive tissue (scar tissue) which blocks conduction. Thus, all energy-based surgical ablative treatments for the treatment of atrial fibrillation attempt to provide lines of conduction block in atrial tissue without the need to cut the tissue and sew it back together. The effective ablative treatments create permanent conduction block by the same mechanism as the cut-and-sew technique: a scar is eventually formed that forms a line of block across the entire thickness of the atrial wall.

For heat-generating ablation technologies, the size and shape of the lesion created is defined by the volume of the tissue heated to 50°C and above. Expressed in another way, the 50°C isotherm forms the boundary of the lesion created by such technologies. For normothermic patients, this corresponds to a 13°C increase in local tissue temperature. For safety reasons, none of the heated tissue should be heated to above 100°C, since the steam so created can disrupt the tissue, or even cause an atrial wall perforation. This constraint limits both the power levels and power application times for the energy heating the tissue. In summary, tissue must be heated by at least 13°C to be effective, but safety concerns limit heating to 63°C for normothermic patients. Since safety is the most important design constraint for ablation devices, this relatively narrow therapeutically effective window can result in ablation designs that are ineffective under some operating conditions. One design strategy that addresses this issue is to use local surface temperature to control energy delivery to the tissue. At least theoretically, this strategy would be especially effective for ablation technology that creates the hottest tissue temperatures near the tissue surface. This approach enables more aggressive applications of energy to heat the tissues while avoiding potentially dangerous overheating situations. The superior results with the technology using RF heating with temperature control tend to validate that approach to ablation device design.

For all heat-generating ablation technologies, the size and shape of the lesion created is determined by both the direct heating pattern of the tissue by the ablating device and by passive heat conduction from the hotter regions of the directly heated tissue to cooler less strongly heated regions. Heat conduction results in larger lesions than could be created by heat deposition patterns alone. With the exception of bipolar ablation technologies, all the heat-generating technologies currently on the market have more than a 5 to 1 variation in deposited power within 2 mm of the tissue surface through which the power enters. For all such technologies, lesion dimensions are extended well beyond 2 mm by heat conduction from tissues heated above 50°C. Although lesion growth by heat conduction is a much slower process than the process of heating tissue directly by tissue absorption of the applied energy, heat conduction results in a lesion volume more than 10 times larger than would occur by heat deposition alone as long as energy is applied long enough. Lesions created quickly, such as those created by bipolar RF devices, have less thermal spread of the lesions than for lesions created with longer applications of energy. Thus, short energy application times can and do result in gaps in lesions, even for bipolar systems. The gap in the lesion can result from a lesion that is not transmural at a given site or even from a short length of non-ablated tissue resulting from the ablation device not contacting the tissue surface.

The most widely applied technology in use today for surgical AF therapy is RF bipolar ablation. Properly designed bipolar ablation devices can achieve reliable transmural epicardial lesions that isolate pulmonary veins. However, as our META analysis shows, clinical results with this type of technology appears to produce inferior success rates for AF therapy applied to patients with non-paroxysmal AF. The technology suffers from a limited lesion set that can be achieved off bypass and some versions of the bipolar devices do not appear to create reliable isolation of the pulmonary veins in patients, at least for single or double RF power applications. For example, three clinical papers report that on average, more than two bipolar RF ablation applications were required to achieve acute conduction block of the right pulmonary veins and more than two bipolar RF ablation applications were required to achieve conduction block in the left pulmonary veins [68, 88, 89].

Our META analysis showed remarkably large differences in pacemaker implantation rates for patients treated with the different ablation technologies: from a low of 2.2% for patient treated with devices using RF with temperature control to the very high pacemaker implantation rates of 17.2% for patients treated with microwave technology and 13.5% for those treated with cryoablation. Authors reporting the high

pacemaker implantation rates cite a number of possible reasons for those high rates, including 1) sick sinus diseases may have been masked by long-standing persistent AF in some patients and 2) overly aggressive beta-blocking medication to limit ventricular tachycardia may have resulted in ventricular bradycardia when patients converted to a regular atrial rhythm. However, the META results presented in this paper tend to weigh against such explanations; for example, the pacemaker implantation rate for ablation devices using RF with temperature and RF without temperature control had a higher percentage of non-paroxysmal AF patients in their treatment groups than the cryoablation group, but both RF groups had a reported pacemaker implantation rate more than 50% lower than the cryo groups. A more likely explanation for the increased pacemaker implantation rates for the cryoablation group is related to the ablation technology itself: the very wide lesions created by the argon Cryo system has an increased chance for affecting the three small epicardial arteries supplying blood to the SA node and the wide Cryo lesions have an increased chance of damaging the AV node.

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