Surgical treatment of atrial fibrillation using radiofrequency ablation
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CHAPTER 2

Surgical treatment of atrial fibrillation; a systematic review

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Abstract

**Background:** The recently published overwhelming number of publications on the surgical treatment of AF, using a wide variety of techniques, blurred any precise appreciation of the nowadays surgical treatment of AF. As a consequence, the "state of the art" of the surgical technique of AF is ill-defined.

**Objectives:** In this review the efficacies of the alternative sources of energy (radiofrequency, microwave and cryo-ablation; group I) and the classical "cut and sew" Cox-Maze III (group II), which claims a 97-99% SR success rate, were evaluated in the surgical treatment of AF.

**Methods:** A computerized search in the PubMed and Medline database was conducted. Only original, English written, clinical manuscripts on the surgical treatment of AF using an alternative source of energy or the classical "cut and sew" Cox-Maze III technique, citing the clinical outcome, including the postoperative SR, were included. The following data were registered: the absolute numbers and percentages of treated patients, gender (male versus female) distribution, type of arrhythmia (permanent- or paroxysmal AF), type of surgery (mitral- or non-mitral valve or a lone AF surgical procedure), postoperative morbidity (bleeding, the use of an intra-aortic balloon pump, cerebral vascular accident) and the postoperative pacemaker implantation-, 30-day mortality-, survival- and SR conversion rates. The mean values for age (years), left atrial diameter (millimeters), preoperative duration of AF (years) and left ventricular ejection fraction (%) were also recorded.

**Results:** Forty-eight studies were included comprising 3832 patients; 2279 in group I and 1553 in group II. The mean duration of AF, left atrial diameter and LVEF were 5.4 versus 5.5 years (p=0.90), 55.5 versus 57.8 millimeters (p=0.23) and 57 versus 58% (p=0.63). The postoperative SR rates for group I and II were 78.3% versus 84.9% (p=0.03). The "cut and sew" Cox-Maze III was conducted in younger patients (55.0 versus 61.2 years; p=0.005), more often to treat paroxysmal (22.9% versus 8.0%) and lone AF (19.3% versus 1.6%) Alternative sources of energy were predominantly used to treat permanent AF (92.0%), almost always as a concomitant surgical procedure (98.4%) and increasingly in combination with non-mitral valve surgery (18.5%). After correction for these variations, the postoperative SR conversion rates for group I and II did not differ significantly anymore (p=0.260).

**Conclusion:** We could not identify any significant difference in the postoperative SR conversion rates between the classical "cut and sew" and the alternative sources of energy, which were used to treat atrial fibrillation.

1 Keywords: atrial fibrillation, radiofrequency, microwave, cryoablation, maze, electrophysiology.
CHAPTER 2

Introduction

The Cox Maze III procedure is a precisely defined pattern of bi-atrial incisions, in order to eliminate AF. This procedure aims to interrupt the multiple wavelet macro reentry circuits, which perpetuate AF. The reported SR conversion rate after the Cox-Maze III procedure is 97-99% and is therefore considered the golden standard (1, 2). The major indication for the “cut and sew” Cox-Maze III surgery, as published by Cox and associates, was intolerance for anti-arrhythmic medication and medically refractory arrhythmia. Main symptoms in this series were dyspnea on exertion, easy fatigability, lethargy and malaise. In addition to that, 17% (60/346) of the operated patients had at least one episode of cerebral thromboembolism. Contraindication in this series was the presence of significant left ventricular dysfunction and a concomitant cardiac or non-cardiac disease. The postoperative pacemaker implantation rate was 15%. Postoperative AF occurred in 11% (38/346) patients during the first 3 postoperative months (1, 2). The complexity of the “cut and sew” Cox-Maze III technique is considered a major drawback. Therefore, this procedure is not universally accepted as a standard practice in the surgical treatment of AF. As a consequence, alternative sources of energy, such as radiofrequency, microwave and cryoablation, have emerged to surgically treat AF. But, the efficacy of the alternative energy sources is debated, because the creation of continuous linear transmural atrial lesions, which act as an electrophysiological conduction block, is considered to be doubtful. In this review the efficacies of the alternative sources of energy (radiofrequency-microwave and cryo ablation; group I) and the classical “cut and sew” Cox-Maze III (group II), which claims a 97-99% SR success rate, were evaluated in the surgical treatment of AF.

Methods

Selection of studies

A computerized search in the PubMed and Medline database was conducted over the period 1980 and March 2004. Keywords, used in the title heading, were Maze, radiofrequency or microwave or cryo-, ultrasound- or laser ablation and atrial fibrillation and surgery. Only original, English written, clinical articles on the surgical treatment of AF, citing their outcome including the postoperative SR conversion rate, were included. Publications reporting on the “cut and sew” technique of the left atrium only, e.g. the so called “mini Maze” operation, were excluded because this surgical technique did not meet the definition of a classical Cox-Maze III procedure nor of an alternative source of energy. Animal or in-vitro experimental studies, case reports and review manuscripts were excluded. Papers which contained previously reported patients’ groups from the same surgical group were also excluded, to avoid double patients counting. Cardiological papers reporting on percutaneous performed procedures were also excluded. Articles reporting on cryoablation were only considered in our analysis when linear continuous atrial lesions were conducted.

Data extraction

The most recent publication using the last postoperative results was extracted if multiple publications were available from the same surgical institute. The following data were extracted from each included study: numbers and percentages of treated patients, gender (male versus female) distribution, the type of arrhythmia (permanent- or paroxysmal AF), type of surgery (mitral valve, non-mitral valve or a lone AF surgery), postoperative morbidity (bleedings, intra-aortic balloon pumps, cerebral vascular events), postoperative pacemaker implantations, 30-day mortality, survival- and sinus rhythm conversion rates. The mean values for age (years), left atrial diameter (millimeters), preoperative duration of AF (years) and left ventricular ejection fraction (%) were also recorded. We have assessed the SR conversion rates and not the “out of AF” rates. The ECG was the examination of choice in all considered publications to establish the postoperative rhythm.
Statistical analysis
For dichotomous parameters (gender, sinus rhythm conversion, bleeding, cerebral vascular accidents, intra-aortic balloon pump, 30-day mortality) a percentage per study was calculated by dividing the absolute number of events by the total number of patients. Heterogeneity in outcome events was tested using the Chi-square test. Since the chi-square test indicated significant heterogeneity between the studies, the calculated percentages were averaged by adding the percentages of all studies divided by the number of studies. This approaches a random effect method, which was also applied for the computation of means of continuous parameters. The means and mean percentages were compared between the two intervention groups (group I: alternative, group II: cut and sew) using the independent t-test or a Mann-Whitney test in case of a skewed distribution. The relation between sinus rhythm conversion and the intervention method was also evaluated with meta-regression. In this model adjustments were made for potential confounders. An arcsine transformation was used for the outcome sinus rhythm conversion to stabilize the variance.

Results
Description of studies
Only publications after 1995 were found. The number of original clinical publications containing the words Maze and atrial fibrillation in the title heading were 90. The numbers of publications concerning the treatment of AF using RF, microwave, cryo, ultrasound and laser were 484, 22, 85, 4 and 6. The numbers of articles, which were eligible for our analysis, were 48; 19 for RF, 5 for microwave, 6 for cryo, 0 for ultrasound and laser (3-32), 16 for the “cut and sew” classical Cox-Maze III (33-49). Two publications reported both on cryo, respectively RF, and the “cut and sew” technique (28, 49). The total number of patients with alternative sources was 2279 (59%) and for the cut and sew 1553 (41%). Subdivided for the alternative sources the total number of RF patients was 1652 (73%), 281 (12%) microwave, 346 (15%) cryo. Irrigated RF was used in 465 patients (28%) whereas 1187 (72%) used temperature controlled RF. The patients' characteristics, type of arrhythmia and surgery,

Main outcome
The mean duration of AF, left atrial diameter and LVEF were 5.4 versus 5.5 years (p=0.90), 55.5 versus 57.8 millimeters (p=0.23) and 57 versus 58% (p=0.63). The postoperative SR rates for group I and II were 78, 3% versus 84.9% (p= 0.03). However, the “cut and sew” Cox-Maze III was conducted in younger patients (55.0 versus 61.2 years; p=0.005), more often to treat paroxysmal (22.9% versus 8.0%; p= 0.05) and lone AF (19.3% versus 1.6%) and the SR conversion rate was below the expected 97-99%. Alternative sources of energy were predominantly used to treat permanent AF (92.0%), almost always as a concomitant surgical procedure (98.4%) and increasingly in combination with non-mitral valve surgery (18.5%). Meta regression showed that the occurrence of postoperative SR was related to the type of arrhythmia (permanent versus paroxysmal; p=0.004) and type of surgery (lone AF versus non-lone AF; p= 0.001) if these parameters were tested univariately. Therefore, we adjusted for type of arrhythmia and type surgery in a meta- regression analysis, which revealed a non-significant difference in the postoperative SR conversion rate (p= 0.260). A clear relationship between postoperative SR and atrial lesion pattern could not be established. The SR conversion rates for the biatrial- versus the left atrial lesion pattern were 83.2% versus 77.5%. Univariate analysis revealed a potential relationship (p=0.05) between the type of lesion pattern (left versus biatrial) and the postoperative SR conversion rate, but this potential statistically significance disappeared in a multivariate analysis (p=0.69). The postoperative complication- and pacemaker implantation rates for group I and II are shown in table 2.1. Thirty day- mortality was 4.2% versus 2.1% (p= 0.09).
Table 2.1 Patients' characteristics, operative procedures and outcome

<table>
<thead>
<tr>
<th>Alternative sources</th>
<th>CS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs; mean)</td>
<td>61,2</td>
<td>55</td>
</tr>
<tr>
<td>Duration AF (yrs; mean)</td>
<td>5,4</td>
<td>5,5</td>
</tr>
<tr>
<td>Left atrial size (mm; mean)</td>
<td>55,5</td>
<td>57,8</td>
</tr>
<tr>
<td>LVEF (%; mean)</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Chronic AF (%)</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>Lone AF (%)</td>
<td>1,6</td>
<td>19,3</td>
</tr>
<tr>
<td>Biaatrial LP (%)</td>
<td>30,3</td>
<td>100</td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>4,4</td>
<td>4,9</td>
</tr>
<tr>
<td>IABP (%)</td>
<td>2,4</td>
<td>2,5</td>
</tr>
<tr>
<td>CVA (%)</td>
<td>1,6</td>
<td>0,5</td>
</tr>
<tr>
<td>30-d Mortality (%)</td>
<td>4,2</td>
<td>2,1</td>
</tr>
<tr>
<td>PM (%)</td>
<td>4,9</td>
<td>5,8</td>
</tr>
<tr>
<td>SR (%)</td>
<td>78,3</td>
<td>84,9</td>
</tr>
</tbody>
</table>

Legends: yrs=years, mm=millimeters, LVEF=left ventricular ejection fraction, AF=atrial fibrillation, LP=Lesion pattern, IABP=intra-aortic balloon pump, CVA=cerebral vascular accident, PM=postoperative pacemaker implantation, SR=postoperative sinus rhythm.

Discussion

The hypothetic sequence of events after the surgical treatment of AF includes the abolition of AF, enabling the sinus node to regain its activity, permitting the restoration of the atrial contractility with associated atrial kick which will improve the left and right ventricular filling during the late diastolic phase, optimizing the cardiac output and performance. As a consequence, an improved quality of life and survival and a decrease in cerebral vascular events can theoretically be anticipated. Each preceding element of the described sequence is a prerequisite for a successful next consecutive step. Obviously, any single study is unable to answer all these consecutive elementary questions at once. Therefore the only endpoint of all the included studies was the restoration of SR, evaluating the efficacy of the surgical technique.

The recently published overwhelming number of publications on the surgical treatment of AF, using a wide variety of techniques, blurred any precise appreciation of the nowadays surgical treatment of AF. As a consequence, the "state of the art" of the surgical technique of AF is ill-defined. This systematic review was conducted to evaluate the English written literature concerning the surgical therapy of AF. All included studies were observational non-randomized studies lacking any control patients groups, although 2 studies compared cryo respectively RF and the "cut and sew" technique to each other (28, 49). The factors which were considered included patients' characteristics, type of arrhythmia (paroxysmal versus permanent), type of surgery (mitral valve- versus non-mitral valve surgery or lone AF versus concomitant surgery) and lesion pattern (left versus bi-atrial lesion pattern). Analysis revealed a heterogeneity of the recruited study patients and their treatment, mandating several statistically adjustments, as performed in this review, to enhance the interpretation of the outcome data.

In our opinion, this systematically review is valuable because the presented data will hopefully facilitate the process of sound clinical judgment of the various surgical techniques, which are used to
treat AF. So, for each result derived from this systematic review the question should be answered whether the preexistent patients' heterogeneity automatically induced the expected clinical result or whether the difference occurred unexpectedly.

**Patients' characteristics**
This study revealed a significant and unexpected difference in mean age of 6.2 years for the group I and II patients; 61.2 versus 55.0 years. As a consequence, the anticipated postoperative morbidity and mortality for both groups will be different. The mean difference in Euro score was 1 point. The duration of AF and left atrial size were similar, which theoretically would provide a comparable base to evaluate the postoperative success rate.

**Postoperative SR conversion rate**
The primary endpoint in all studies was postoperative SR conversion. The mean postoperative SR rates for group I and II were 78.3% versus 84.9% (p = 0.03). Although the preoperative duration of AF and the size of the left atrium was similar for both groups, this difference in favor of the "cut and sew" group can be potentially explained by the substantially higher incidence of paroxysmal AF in group II; 8.0% versus 22.9%. In general, paroxysmal AF is better amendable for any therapy than permanent AF. In addition to that, the mere occurrence of SR on a standard surface ECG can not be considered an appropriate definition of success, as was conducted in all, but one, of the evaluated studies. Only Loennerholm reported an improved quality of life appreciation in 18 patients with paroxysmal AF (41). All other studies failed to provide any information on the postoperative "burden of AF" which includes an evaluation of the number and duration of AF episodes as well as the subjective intensity of each episode associated with its clinical manifestation, such as shortness of breath, perspiration, level anxiety. As consequences this omission was a major drawback of all studies.

A second major difference between group I and II patients, potentially affecting the postoperative SR conversion rates, was the incidence of lone AF. Lone AF was the primary indication in 19.3% in group II, whereas in group I only 1.6% of the patients had a lone AF surgery. Lone AF treatment, especially in patients below 60 years of age, is associated with excellent results. So, in summary the 6.6% difference SR conversion rate in favor of the "cut and sew" can not unequivocally be attributed to the superiority of the efficacy of "cut and sew" surgical technique.

Experienced surgical groups including McCarthy, Schaff, Arcidi and Jessurun who precisely performed the "cut and sew" Cox-Maze III procedure reported a SR success rate of 90.4%, 85%, 87.4% and 88%. These groups were unable to duplicate the 97-99% SR conversion rate (42-44, 48).

**Postoperative mortality**
The postoperative mortality in group I is double as high as in group II; 4.2% (83/2207) versus 2.1% (p=0.09). But the difference in mean euro score due to the mean age difference is at least 1 point. In addition to that, a concomitant cardiac procedure was performed more often in the group I patients; 98.4% versus 80.7%. Obviously a higher expected mortality can be anticipated for the group I patients.

**Pacemaker implantation**
This study revealed a small difference in postoperative pacemaker implantation in favor of the group I patients; 4.9% versus 5.8% (p=0.21). But the interpretation of this finding is blurred due to the variable investigator and time dependant indication of pacemaker implantation. Obviously a sick sinus syndrome is a proper and absolute indication. But the various studies also reported an AV junctional, an atrypical bradycardic arrhythmia or the lack of an exercise- induced SR tachycardia as a relative indication for pacemaker implantation. The postoperative time interval was variable and certain groups were more aggressive in theirs indication while others adopted a more conservative approach. This certainly influenced the eventual postoperative pacemaker rate. Whether the "cut and sew"
technique is a risk factor for a sick sinus syndrome due to devascularisation and denervation of the sinus node remains a matter of debate.

**Postoperative morbidity**
The postoperative bleeding rates in both groups were similar although the "cut and sew" technique includes multiple atrial incisions which theoretically increased the risk of postoperative bleeding. Postoperative cerebral vascular accident rates in both groups were equal. So, the presumed advantage of negligible cerebral vascular event rate in the group II is not solitary confined to this subset of patients. Low cardiac output, expressed by the use of the intra aortic balloon pump was similar. But groups II were basically younger patient and had more often a lone AF procedure. So, there tends to be an increased risk for the use of an IABP in the group II patients.

**Lesion transmurality and SR conversion rate**
The main difference between the classical “cut and sew” Cox-Maze III procedure and the alternative sources of energy is the uncertainty of the continuity and transmurality of the induced atrial wall linear lesions. The difference in postoperative SR conversion rate for the group I patients, who had a bi-atrial lesion pattern, and the “cut and sew” group II patients was 6.6%; 78.3% versus 84.9% (p=0.03). A potential explanation for this small but distinct difference is the lack of continuous and transmural atrial lesions. However, the necessity of histologically proven transmural lesion as a prerequisite to achieve SR is still debated. Santiago and colleagues who correlated the intra-tissue temperature with the tissue thickness and with the histological appearance of lesions in 10 mitral valve patients, found a transmural lesions in only 20% (2/10), a variable myocardium damage in 30% (3/10) and only endocardial damage in 50% (5/10). At 6 months, 4 out 5 patients with a myocardial, but non-transmural lesions, were still in SR and even 2 of the 5 patients, who only had an endocardial lesion converted in SR (50). This finding suggests that even non-transmural lesions are associated with SR conversion. Pappone, who conducted circumferential pulmonary vein orifices isolation in 589 patients, of whom 31% had a chronic AF, reported a SR conversion rate of 80% (51). This finding corroborates the finding of Chen, who showed that the pulmonary veins itself can be a substrate for easier induction and maintenance of AF (52). Jalife postulated that in some case, AF is organized by one or a small number of high- frequency sources localized in the left atrium, indicating that targeting these sources might prevent the formation of reentrant sources, eliminating AF (53).

**Left versus bi-atrial lesion pattern in relation ship to the SR conversion rate**
A clear relationship between postoperative SR and atrial lesion pattern could not be established. The SR conversion rates for the biatrial- versus the left atrial lesion pattern were 83.2% versus 77.5%. Univariate analysis revealed a potential relationship (p=0.05) between the type of lesion pattern (left versus biatrial) and the postoperative SR conversion rate, but this potential statistically significance disappeared in a multivariate analysis (p=0.69). This indicated that the left atrial lesion pattern appeared as efficacious as the bi-atrial lesion pattern. So, the concept of "trigger and substrate" with left atrium as the predominate site for atrial fibrillation still remains valid (54), although Konings and associates, suggested that both atria as a whole participate, although not equally, in the perpetuation of the fibrillatory process (55). Nair observed that the induced AF in patients with rheumatic heart valve disease show a rapid organized arrhythmia with earliest atrial activity in the coronary sinus orifice and isthmus. Targeting these regions of the coronary sinus orifice was associated with a successful suppressing of the arrhythmia (56). Waldo postulated that there is a major interaction between fibrillation and flutter, indicating that AF is usual required for the deovelopment of a line of functional block between the vena cavae, which in turn is required for the development of atrial flutter, which
in itself can provoke a fibrillatory conduction and therefore maintaining AF (57). Nevertheless, it appeared that the left atrial lesion pattern was effective in the abolition of AF.

Limitations of the study
A couple of confounding factors, which potentially can affect the interpretation of the data, can be identified. The unavailability of prospective randomized studies on the surgical treatment of atrial fibrillation was a drawback of this systemic review. Each of the various energy sources, radiofrequency, microwave and cryo ablation, has its own specific ablative characteristics on the atrial tissue, which barely can be quantified and were therefore not considered in this review. The performed ablation pattern in the various studies using alternative sources of energy could only be distinguished between a left- versus bi-atrial lesion pattern. A bi-atrial lesion pattern was conducted in 815 group I patients, whereas 1422 group I patients had a left atrial lesion pattern. Patients who had a solitary left atrial lesion pattern showed a broad variety of ablation lines within the left atrium, which might had an impact on the outcome of this review. Nevertheless, we felt it was still worthwhile and appropriate to classify and categorize the patients, as we have done in this review. The heterogeneity of the various included studies was addressed using a statistical regression correction in order to enhance the comparison of the data of the various studies. It was our opinion that this approach was considered the best alternative to review the international literature.

In conclusion, we could not identify any significant difference in the postoperative SR conversion rates between the classical "cut and sew" and the alternative sources of energy, which were used to treat atrial fibrillation.
Table 2.2 Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Atrial Lesion</th>
<th>Bleeding</th>
<th>Postoperative AF</th>
<th>LA Diameter</th>
<th>LVEF</th>
<th>Mitral Valve Disease</th>
<th>Left Atrial Diameter</th>
<th>Duration of AF</th>
<th>Follow-up</th>
<th>Control Group</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Yes</td>
<td>No</td>
<td>6 months</td>
<td>2.8 cm</td>
<td>65%</td>
<td>No</td>
<td>3 cm</td>
<td>1 year</td>
<td>100 patients</td>
<td>Yes</td>
<td>Bi-atrial lesion pattern</td>
</tr>
<tr>
<td>Study 2</td>
<td>Yes</td>
<td>Yes</td>
<td>9 months</td>
<td>3.1 cm</td>
<td>55%</td>
<td>Yes</td>
<td>4 cm</td>
<td>2 years</td>
<td>120 patients</td>
<td>No</td>
<td>Bi-atrial and Bi-ventricular lesion pattern</td>
</tr>
</tbody>
</table>

Legends: AS = Alternative source of energy; CS = Cut and Sew; n = number of patients; yrs = years; Dur = duration of AF; LA = left atrial diameter; LVEF = Left ventricular ejection fraction; MV = Mitral valve disease; NMV = Non-mitral valve disease; Lone = Lone AF; BP = Biatrial lesion pattern; Ble = Postoperative bleeding; IABP = Intra aortic balloon pump; CVA = Cerebral vascular accident; SR = Sinus Rhythm; av = available patients; PM = Pace maker
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