Radiofrequency Ablation of Paroxysmal Atrial Fibrillation: Factors Determining Long-Term Clinical Efficacy

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Summary

Background: Most of the studies on this subject have reported predictors of recurrence of atrial fibrillation after catheter ablation with relatively short follow-up periods.

Objective: To retrospectively evaluate predictors of long-term recurrence of paroxysmal atrial fibrillation (AF) in patients undergoing pulmonary vein isolation following one single procedure.

Methods: The authors studied a total of 139 patients (102 men; mean age of 55 ± 12 years) undergoing radiofrequency ablation using the ostial or extra-ostial techniques for left atrial approach, combined or not with cavotricuspid isthmus ablation (CTI). Pre, intra and post-ablation variables were evaluated using univariate and multivariate analyses to determine the predictors of recurrence of AF after one procedure.

Results: After a 33 ± 12-month follow-up, we observed that a longer time of history of AF, use of more antiarrhythmic drugs, and recurrence of AF within 60 days post-procedure increased the risk of long-term recurrence of AF. On the other hand, the association of atrial flutter and concomitant CTI ablation reduced the risk of recurrence of AF.

Conclusion: Clinical variables such as time of history of AF and a larger number of antiarrhythmic drugs already used influenced the outcomes of catheter ablation. In patients with associated atrial flutter, simultaneous CTI block significantly reduced the long-term recurrence of atrial fibrillation. (Arq Bras Cardiol 2008; 90(2):112-118)

Key words: Atrial fibrillation; catheter ablation; recurrence; follow-up studies.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, with growing prevalence in the past decades[1], and is responsible for a significant increase in morbidity and mortality of the general population[2], mainly when associated with comorbidities such as heart failure and left ventricular dysfunction[3].

Since Haissaguerre et al[4], Jais et al[5] and Shah et al[6] called attention to the importance of pulmonary veins in the initiation of episodes of AF, several studies have sought to determine the best technique to be used in the non-pharmacological treatment of this arrhythmia, as well as to show which factors can predict a higher chance of recurrence after these procedures. The literature shows varying result[7-10], both because of differences in patient selection and because of the efficacy of these techniques[9,11,12]; thus, there is no consensus as to which is the best therapeutic option for the control of AF patients. Also, most of these studies show results after more than one intervention and with usually short follow-up periods, thus possibly overestimating the procedural success.

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Objective

To investigate the long-term predictors of recurrence of paroxysmal AF in patients undergoing radiofrequency ablation after one single procedure.

Patients and methods

Study population - A total of 139 consecutive patients (102 men; mean age of 55±12 years) undergoing pulmonary vein isolation using the ostial or extra-ostial technique were studied between May 2001 and July 2004. All had paroxysmal AF, were highly symptomatic, and had frequent paroxysms of arrhythmia despite having received 2±1 antiarrhythmic drugs. The patients had a history of AF for 6±5 years, and only 7% had a structural heart disease.

Study protocol - The study protocol was approved by this Institution's ethics committee and a written informed consent was obtained from all patients before the procedure.

Patients receiving warfarin were advised to discontinue the drug at least five days prior to the procedure, and were then

maintained with subcutaneous sodium enoxaparin at a dose of 1mg/kg every 12 hours, which was discontinued 12 hours prior to ablation. Blood was collected for determination of prothrombin time aiming to achieve an INR lower than 1.8 . Patients underwent transesophageal echocardiogram to confirm the absence of intracardiac thrombi. After an eight-hour fast, they were sent to the electrophysiology laboratory and underwent deep sedation with intravenous propofol, midazolam and fentanyl controlled by an anesthesiologist. The airway was kept open using orotracheal intubation or a laryngeal mask. Non-invasive blood pressure monitoring, pulse oximetry and measurement of exhaled CO_2 were also used. Three multipolar catheters were introduced and positioned via right femoral vein punctures: one decapolar catheter (Irvine, Daig - St.Jude Medical's or Johnson & Johnson) in the coronary sinus; one circular decapolar catheter (Lasso, Biosense Webster) in the left atrium via a patent foramen ovale or transeptal puncture; and one quadripolar ablation catheter with a 2-mm inter-lead spacing and a 4-mm or 8-mm distal lead (EPT-Boston Scientific or Johnson & Johnson) also in the left atrium via a second transeptal puncture. The Lasso catheter positioning was guided by angiography of the pulmonary veins (PV) using contrast medium (meglumine ioxalate 32.5g/100ml), except for the right inferior veins in which it was not systematically used. Anatomical determination of the PV was made using fluoroscopy, and images were obtained with a Fisher (Fisher Electrophysiology X-Ray Imaging System) or General Electric equipment (OEC Series 9800plus), in left and right anterior oblique views (30°-45°). Surface electrocardiogram and bipolar intracardiac electrograms, filtered in the range between 50 and 500 Hz, were obtained and recorded in digital system (Electrophysiologic Measurement System – EMS – The Netherlands or EP-Tracer V 0.771- Cardiotek – The Netherlands). Programmed atrial and ventricular pacing were routinely performed to rule out other concomitant arrhythmias.

The 63 initial patients, between May 2001 and February 2003, underwent ostial ablation with the purpose of obtaining electric PV isolation. After the transeptal punctures, 10000IU of intravenous heparin were administered. After 15 minutes, the activated clotting time (ACT) was measured and repeated every hour. Supplementary heparin doses were administered with the purpose of keeping the ACT between 250 and 300 seconds. Mapping was guided by a 15-mm diameter Lasso catheter placed approximately 5mm inside each PV approached, thus permitting the recording of veno-atrial potentials. A 4-mm catheter was used for ablation; it was directed toward the Lasso bipole which recorded the earliest venous potential. RF pulses were then delivered in the ostium in order to disconnect these potentials (Figure 1). When this was achieved, the ablation catheter was displaced to earlier connection points, until potential isolation was completed. Even if disconnection had already occurred, pulses were delivered until the whole vein circumference was completed. RF deliveries were limited - approximately 30Watts, 50°C -, for 30 to 60 seconds.

The 76 subsequent patients, between February 2003 and July 2004, underwent extra-ostial circumferential ablation, also with the purpose of obtaining electric isolation of PV. After venous puncture, 5000 IU of heparin were administered, followed by 5000IU more for each transeptal puncture, aiming to keep the ACT>300 seconds, with repeated doses every half hour.

A 20 to 25-mm diameter Lasso was placed in a more extra-ostial position, in the PV antrum, thus delimiting the area to be cauterized. RF pulses were delivered around the circular catheter, with the 8-mm ablation catheter being slowly displaced linearly around it for a 5 to 20-mm distance from the ostium, thus avoiding direct contact with Lasso. Deliveries were limited to between 50 and 60 Watts, 50 to 60°C, and lasted between 40 and 60 seconds, in an attempt to perform circumferential ablation and achieve PV isolation.

Regardless of the technique used, in patients with previously recorded atrial flutter or in whom atrial flutter had been induced during the procedure, a cavotricuspid isthmus (CTI) block was performed using the same ablation catheter, that is, a 4-mm catheter in the ostial approach or 8mm in the extra-ostial approach.

After the procedure, the patients were kept on bedrest for a period of at least six hours. Low-molecular-weight heparin was started six to eight hours after the end of the procedure and continued after hospital discharge, until oral anticoagulation had achieved adequate therapeutic levels. Oral anticoagulation was maintained for a period of at least 30 days. A 12-lead electrocardiogram was performed after the procedure and on the day after. Patients were discharged after an observation period of at least 24 hours.

Antiarrhythmic drugs were maintained at hospital discharge, when immediate recurrences or symptomatic extrasystoles were present. These drugs were usually discontinued by the patient's physician.

Variables analyzed - For the analysis of predictors of long-term recurrence, the variables studied were grouped in classes as follows:

a) *Pre-ablation* - gender, age, time of AF, associated atrial flutter, other associated diagnoses (diabetes, hypertension, valvular heart disease, structural heart disease), left atrial size, left ventricular ejection fraction, previous cardioversion (electrical, chemical, or both), and number of medications previously used.

b) *Intra-ablation* - ostial or extra-ostial approach, flutter ablation, catheter for flutter ablation, power, temperature and time of delivery, number of veins approached and disconnected, and time of procedure and fluoroscopy.

c) *Post-ablation* - time for recurrence shorter than or longer than 60 days.

Endpoints

Recurrences, whether symptomatic or not, were classified as early recurrences (within the first 60 days) or late recurrences (after the first 60 days post-ablation), and were discriminated as recurrence of fibrillation, flutter or atrial tachycardia. In order to construct the curve of events, only the cases of AF occurring within the first 60 days, but that also persisted beyond this period, or those occurring at any time

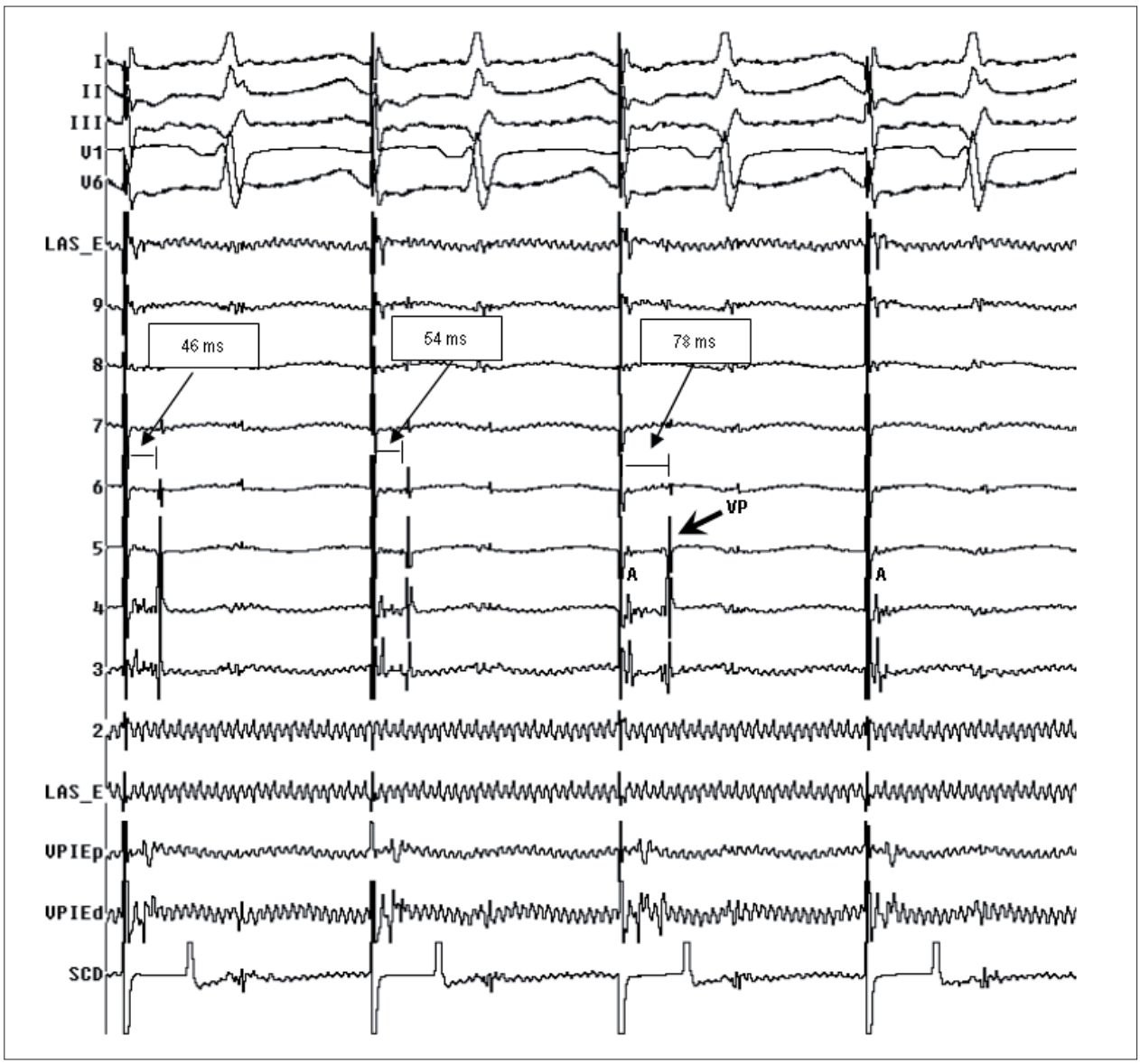


Fig. 1 - Vein potentials disappear during radiofrequency delivery. From the first to the third beat, a progressive increase (46, 54 and 78 milliseconds) of the interval between the atrial (A) and venous (VP) potentials is observed. In the fourth beat, the venous component disappears, thus making the electrical isolation of the pulmonary vein evident.

of the follow-up beyond this initial deadline were adopted as recurrence criteria. Procedural success was defined when the patients did not present recurrence of AF by the end of the follow-up after one procedure, whether receiving antiarrhythmic drugs or not. Patients considered well controlled were those who, despite having had recurrences, had a number of recurrences lower than prior to the procedure, and also those for whom previously ineffective medications were now able to control the paroxysms. Failures were considered when the procedure did not reduce the paroxysms, the arrhythmia became permanent or persistent, when reintervention was necessary, or when permanent pacemaker (PPM) implantation was indicated.

Complications were divided into major or minor complications. Major complications were those requiring longer hospital stay, intervention for treatment, or which resulted in permanent lesion or death.

Follow-up - Patients were reevaluated on an outpatient basis at 30 days, and three, six and twelve months with a 12-lead echocardiogram and 24-hour holter monitoring. After this period, and also for those residing out of the city of Sao Paulo, the follow-up was performed by the patient's physician. The patients were contacted via mail, telephone or telegram until the follow-up period had been completed. An objective questionnaire was sent to the patients, requiring simple and direct answers on the perceived arrhythmia pre and post-

ablation. All patients sent their follow-up electrocardiogram or holter monitoring to our service. Those who had a sensation of palpitation, whether or not with tachycardia, were instructed to record the episodes using an electrocardiogram, holter monitor, or event monitor. When fibrillation, atrial flutter or tachycardia was recorded, reintervention was performed or not according to a joint decision made with the patient and his physician.

Statistical analysis:

Quantitative data are described as mean ± standard deviation. Categorical data were analyzed using the Student's t test or the chi square test. Univariate analysis of the factors possibly associated with long-term recurrence of atrial fibrillation after one procedure, and multivariate analysis to determine independent predictors of risk of recurrence of atrial fibrillation were performed using Cox proportional regression model. The curves of events were compared using the log rank test. The level of statistical significance was set at $p < 0.05$. The SPSS statistical package for Windows version 13.0 was used.

Results

Overview - The 63 (45%) patients undergoing ostial ablation were not significantly different from the 76 (55%) undergoing extra-ostial ablation as regards clinical characteristics (Table 1).

The mean duration of the procedures was 223±49 minutes, with 67±18 minutes of fluoroscopy. On average, the characteristics of the deliveries were: power (45±13 Watts); temperature (52±4°C) and time of delivery (45±14 seconds).

An average of four veins was approached, with isolation of 3±1 veins. They received an average of 16±10 radiofrequency pulses which were distributed as follows: left superior PV (19±11 pulses); right superior PV (18±9 pulses); left inferior PV (12±8 pulses) and right inferior PV (15±11 pulses).

Forty four (32%) patients also underwent CTI block, 19 (43%) of them with a 4-mm catheter and 25 (57%) with an 8-mm catheter. Among the 19 patients, three (16%) had no previous history of atrial flutter. One (4%) patient approached with an 8-mm catheter had no recorded flutter. Four patients with recorded flutter did not have the CTI approached, two in each group.

Table 1 – Clinical characteristics of the 139 patients studied

	Group Ostial (n=63) / 45%	Group Extra-ostial (n=76) / 55%	p
♂/♀(n)	47/16	55/21	0.76
Age (years)	55.61 ± 10.26	55.28 ± 12.72	0.86
Time of AF (years)	6.40 ± 6.01	5.09 ± 4.20	0.13
Associated flutter (n) / %	(16) / 25%	(32) / 42%	0.71
LA (mm)	40.44 ± 5.58	41.67 ± 4.82	0.17
EF (%)	67.24 ± 6.94	66.20 ± 11.04	0.54
No structural heart disease (n) / %	(60) / 95%	(70) / 92%	0.45
No disease (n) / %	(22) / 35%	(36) / 47%	0.14
N° of previous drugs (n)	2.03 ± 1.04	2.03 ± 1.03	0.86
No previous CV (n) / %	(15) / 24%	(13) / 17%	0.28

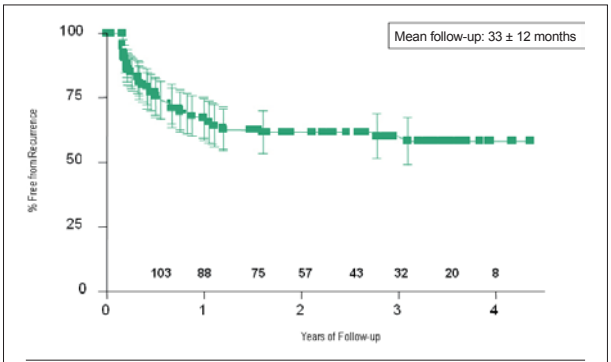
AF - atrial fibrillation; LA - left atrium; EF - ejection fraction; CV - cardioversion; (n) - absolute number.

Recurrences and non-recurrences - During a 33±12-month follow-up after one single procedure, 70 (50%) patients did not present any recurrence. Of the 69 (50%) who had recurrence, six (4%) had an isolated episode of AF within the first 60 days, two (2%) had an isolated episode of AF within 90 days, and nine (7%) had episodes of atrial flutter or tachycardia, whereas 52 (37%) had recurrent paroxysms of AF. Thus, procedural success was achieved in 50% of the patients; 25% became well controlled, and 25% were considered failures. Among the patients with procedural success, 42 do not receive antiarrhythmic drugs, 12 receive beta blockers, and 16 receive class III antiarrhythmic drugs. Among controlled patients, eight are not receiving antiarrhythmic drugs, two receive beta blockers, and 25 receive class I or III antiarrhythmic drugs. Among failures, 30 were referred for a second procedure, two await reintervention, one progressed with permanent AF, and one underwent PPM implantation.

Predictors of recurrence - For the analysis of recurrence-free curves, patients with isolated episodes of AF and those with atrial flutter or tachycardia were added to the group of non-recurrence, when a blanking period of 60 days was assumed (Graph 1). This period is the censorship of recurrences obtained in variable pre-determined periods following ablation, assuming that, in this phase, occasional recurrences do not interfere with late procedural results. Analysis without blanking was also performed. Under this circumstance, those with isolated episodes of AF within the first 60 days were added to the recurrence group.

After considering the blanking period of 60 days, we observed that at three, six, nine, 12, 15, 24 and 57 months of follow-up, 85%, 77%, 71%, 67%, 63%, 62% and 58% of the patients remained free from symptomatic recurrence of AF, respectively.

Using univariate analysis, we observed that: age (p=0.05), time of AF (p <0.001), number of drugs (p=0.021) and associated flutter (p=0.003); delivery power (p<0.054), flutter ablation (p=0.005) and catheter for flutter ablation (p=0.005),



Graphic 1 - Overall curve – free from recurrence.

as well as recurrence within the first 60 days (p<0.001) could influence the recurrence of AF, and were thus used in the multivariate analysis.

In the multivariate analysis, time of AF (p<0.01; relative risk =1.07; 95%CI 1.02 to 1.13) and number of drugs (p=0.02; relative risk=1.32; 95% CI 1.04 to 1.69) proved to be independent factors for a higher risk of late recurrence of AF, whereas the presence of associated flutter (p<0.01; relative risk=0.31; 95% CI = 0.15 to 0.64) was an independent factor of lower risk. Atrial flutter ablation (p<0.01; relative risk=0.39; 95% CI 0.20 to 0.75) and an 8-mm catheter used for flutter ablation (p<0.01; relative risk=0.07; 95% CI 0.01 to 0.48) were predictive of a lower risk of late recurrence of AF. Recurrence within the first 60 days (p<0.01; relative risk=4.95; 95% CI 2.76 to 8.89) remained as an independent factor of a higher risk of late recurrence of AF.

As can be observed in Graph 2, 65% of the patients with less than four years of history of AF had not had any recurrences, versus 48% of those who had had the disease for a longer period of time.

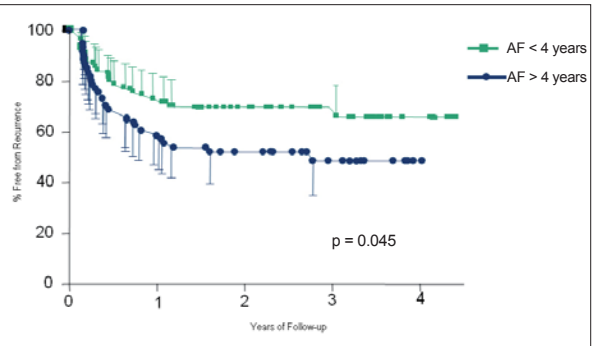
We also observed that among the patients who had previously received three or more antiarrhythmic drugs, only 34% were free from recurrence, when compared with 61% of those receiving fewer medications (Graph 3).

On the other hand, a previous history of flutter reduced the risk of recurrence of AF (relative risk = 0.31), and the use of an 8-mm catheter for ablation of associated atrial flutter reduced this risk even further (relative risk = 0.07). Thus, at the end of the 33-month follow-up, 80% of the patients with flutter associated with AF were observed to be free from recurrence, versus only 48% of those without previous documented AF (Graph 4). Also, for the same follow-up period, 96% of the patients who underwent concomitant CTI ablation with an 8-mm catheter had not had recurrence, *versus* 63% of those undergoing CTI ablation with a 4-mm catheter, and only 46% of those not undergoing this procedure (Graph 5).

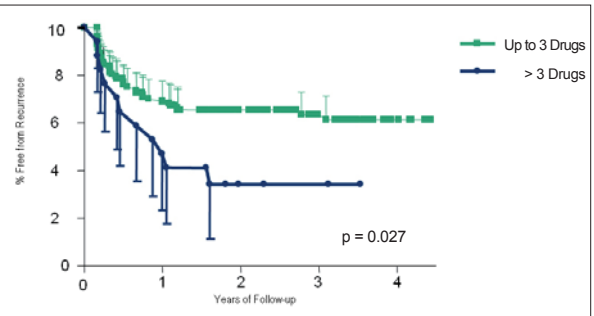
Complications - A total of 116 (83%) patients had no complications, whereas 23 (17%) had some complication, as discriminated above:

a) *Major complications*: one transitory ischemic attack; one acute myocardial infarction in the inferior wall at the end of the procedure, with the patient undergoing successful primary angioplasty; one atrio-esophageal fistula followed by death; five hemopericardia drained during the procedure; one deep venous thrombosis; one pseudoaneurysm surgically corrected.

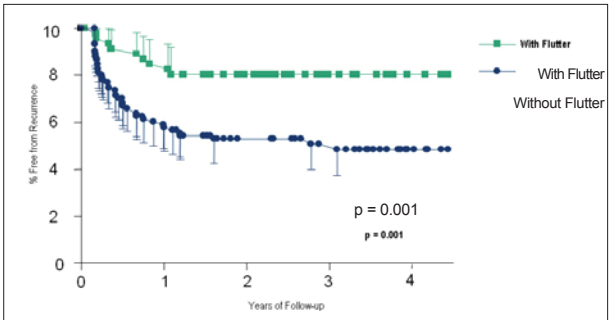
b) *Minor complications*: one phrenic nerve paresis; three PV stenoses with no clinical repercussion; two burns caused by the neutral plate; two transitory ST-segment elevations; two pulmonary congestions within the first week post-ablation; and three large hematomas with spontaneous resolution.



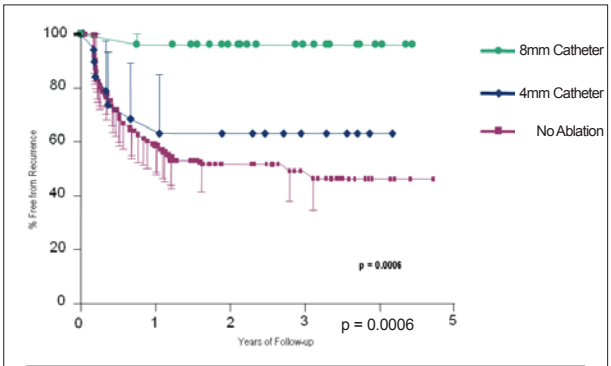
Graphic 2 - Free from recurrence according to time of history of AF (<4 years or >4 years). Data presented with 95% confidence interval (CI).



Graphic 3 - Free from recurrence according to the number of antiarrhythmic drugs previously used (<3 or ≥3drugs). 95% CI.



Graphic 4 - Free from recurrence according to the presence or absence of previous atrial flutter. 95% CI.



Graphic 5 - Free from recurrence according to concomitant CTI ablation – Type of catheter used: 4 or 8 mm. 95% CI.

Discussion

The results of the present study suggest that the long-term response of patients undergoing RF catheter ablation may depend not only on the technique used, but also on the patient's clinical profile. We observed that certain variable characteristics such as time of history of AF and the number of medications previously used interfered in the results.

Even though the concomitance of atrial fibrillation and flutter in the same individual is common, the reason for this occurrence remains uncertain. In this study, the diameter of the catheter and technique used to modify the left atrial substrate did not seem to influence the long-term outcome of the patients. However, when CTI ablation was associated, a positive effect on the final outcome was observed. Since 96% of the patients undergoing this procedure with an 8-mm catheter did not have recurrences and with the 4-mm catheter this rate was 63%, both percentages significantly overlap with the 46% of the patients whose isthmus was not approached.

These observations are in accordance with the results of studies that evidenced the role of CTI. Schemieder et al[13] observed that after CTI block, the rate of occurrence of atrial fibrillation was reduced from 55% to 33%, going from a success rate of 45% to 67%, a value that is close to that found in the present study with a 4-mm catheter (63%). Kumagai et al[14] and Sharf et al[15] studies also showed the advantage of the association of CTI block with ablation of pulmonary focuses. Bottoni et al[16] evidenced a rate of 64% of recurrence of symptomatic arrhythmic episodes after flutter ablation; however, they verified a decrease in the number of episodes and hospitalizations in a group of 56 patients with history of AF.

These observations could leave the impression that only CTI ablation could reduce the chance of recurrence of AF. Nonetheless, Bertaglia et al[17] showed clearly that the recurrence of AF after CTI block alone increases progressively over time. Wazni et al[18] randomized patients with AF and flutter in two groups, one of them only for PV isolation and the other for isolation plus CTI block, and observed, in a follow-up shorter than one year, that isolation alone was able to control both arrhythmias, although isthmus block could prevent the early recurrence of arrhythmias. In the present study, however, the association of isolation and CTI block reduced recurrences also in the long term.

The finding of a success rate lower than that reported in other studies[4,7,9], with variations between 62% and 88%, was also noteworthy in this study. However, these percentages refer to follow-up periods ranging from five to 15 months, which could thus have led to an overestimation of the procedural success. In this study, the follow-up period was of 33 ± 12 months, and this probably led to a lower success rate if compared to the studies mentioned above. Della Bella et al[19] showed a success rate similar to ours, considering a 12-month follow-up period (65% *versus* 67%, respectively). Recently, Cheema et al[12,20] and Lee et al[21] presented their results based on longer follow-up periods that ranged from 11 to 30 months, achieving success rates no higher than 69% in this circumstance. In addition, some of these studies[7,12] consider success rates not only after one procedure, but summing up the positive results obtained after repeated interventions. Like in Cheema et al[20] study, in the present study the success rates were obtained considering only one single procedure, which may also have contributed to a lower success rate.

The most severe complication observed was an atrio-esophageal fistula followed by death of the patient[22]. Up to that moment, this complication of catheter ablation had never been reported in the literature. Contemporaneously with the occurrence observed in this study[22], Pappone et al[23] also described two cases of atrio-esophageal fistula, with death of one of the patients. The higher risk for its occurrence lies in the fact that high energy is delivered, mainly in the left posterior atrial wall. This complication led to the use of an intraesophageal thermometer[24] or to the oral administration of barium contrast, which permits the esophageal position to be delimited[25], thus avoiding deliveries close to the esophagus.

Some limitations of this study should be taken into consideration. One of them is the fact that it was a retrospective study. Another is the consideration that the occurrence of asymptomatic episodes of atrial fibrillation was not actively searched. However, the long follow-up period may probably have attenuated this limitation, since there was a greater chance of spontaneous recording of the arrhythmia.

The high success rate among those undergoing CTI block may result from the fact that these patients had a previous history of flutter associated with AF, and thus a specific subgroup was selected. This technique may not apply to all patients with paroxysmal AF, and the reproduction of these results in prospective studies is required.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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