Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation

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Aims The success rate of circumferential pulmonary vein ablation (CPVA) to treat atrial fibrillation (AF) ranges from 60 to 90%, depending on the series. The objective of the study was to identify predictors of AF recurrence after a standardized CPVA procedure.

Methods and results A series of 148 consecutive patients undergoing CPVA for symptomatic paroxysmal (60.8%), persistent (23.6%), or permanent (15.5%) AF refractory to antiarrhythmic drugs were included in the study. CPVA with the creation of supplementary block lines along the posterior wall and mitral isthmus was performed and a minimum of 6 months follow-up completed in all patients. Structural heart disease was present in 19.6% and hypertension in 33.8% of patients. After 13.1 ± 8.4 months follow-up, 73.6% of patients were free of AF recurrences after a mean of 1.18 ± 0.45 procedures/patient (one procedure in 85.2%, two procedures in 14.8%, and three procedures in 2.7%). Univariable analysis showed that the risk of AF recurrence increases with age (HR 1.03; 95% CI 1.00–1.06, P = 0.031), with the presence of previous hypertension (HR 2.7; 95% CI 1.43–5.07, P = 0.002), and if AF is permanent (HR 2.23; 95% CI 1.05–4.59, P = 0.042). In addition, larger anteroposterior left atrial diameter (LAD) (HR 1.11; 95% CI 1.05–1.18, P = 0.001) and larger left ventricular end-systolic diameter (HR 1.07; 95% CI 1.00–1.15, P = 0.029) prior to the procedure were associated with AF recurrence after CPVA. Cox regression analysis showed that hypertension (OR = 2.8; 95% CI 1.5–5.4; P = 0.002) and LAD (OR = 1.1; 95% CI 1.05–1.19, P < 0.001) were independent predictors of AF recurrence. The mean predicted proportion of patients with AF recurrence after CPVA of the multivariable model showed a linear relationship with the increase in LAD prior to the procedure. The presence of hypertension further increased the mean predicted proportion of patients with AF recurrence at each LAD.

Conclusion Hypertension and LAD are independent pre-procedural predictors of AF recurrence after CPVA to treat AF. These data may help in patient selection for AF ablation.

KEYWORDS
Atrial fibrillation; Ablation; Predictors

Introduction

Unlike electrical cardioversion or antiarrhythmic drugs, pulmonary vein ablation offers the possibility of curing AF. Initially, there was a great variety of different technical approaches, with a low success rate and a relatively high rate of complications. Therefore, the procedure was cautiously reserved for highly symptomatic patients as a ‘last resort’ therapy. However, the ablation procedure has become more standardized in recent years and many centres have reported high success rates and a reduction in complications. In this regard, the patient selection criteria for performing the procedure are less restrictive and the procedure is now indicated for diseased atria.

Circumferential pulmonary vein ablation (CPVA), with the creation of additional lines to prevent macro-re-entrant atrial tachycardia, is a widely used technique for AF ablation. However, the success rate falls short of 100% (~80% in the most recent series of selected patients) and the risk of severe complications remains a matter of concern: severe vascular events in 1%, tamponade/perforation in 0.5%, severe-to-moderate pulmonary vein stenosis in 1.5%, and atrial macro-re-entrant tachycardia in 2%. Thus, not all patients may be suitable candidates for AF ablation and it seems desirable to identify pre-procedural predictors of recurrence that would be useful for defining selection criteria.

To date, investigators have identified some intraprocedural predictors of recurrences for AF ablation, namely, pre-existent left atrial scarring during catheter mapping, voltage abatement, the percentage of left atrium ablated...
study protocol was approved by the hospital’s Ethics Committee.

the basis of their AF duration. Patients were included after mechanical prosthetic heart valve. No patient was excluded on transoesophageal echocardiography, and the presence of a transthoracic echocardiography.

dictor of late AF recurrence in paroxysmal AF. However, has been identified as an independent post-procedural predictor of AF recurrence after left atrial circumferential ablation, and after-segmental ostial ablation. Also, some independent pre-procedural predictors of AF recurrence have been described for segmental ostial ablation, i.e. age >50 years, paroxysmal vs. non-paroxysmal AF. Finally, early AF recurrence has been identified as an independent post-procedural predictor of late AF recurrence in paroxysmal AF. However, pre-procedural independent predictors of AF recurrence have not been described for CPVA. The objective of this study was to identify the clinical and echocardiographic parameters obtained prior to the procedure, which may help to predict AF recurrences after CPVA in a consecutive series of patients.

Methods
Study population

All patients referred to our institution for AF ablation between January 2003 and November 2005 were included in the study. Exclusion criteria were age < 18 or > 75 years, anteroposterior LAD at transthoracic echocardiography > 55 mm, presence of LA thrombus on transoesophageal echocardiography, and the presence of a mechanical prosthetic heart valve. No patient was excluded on the basis of their AF duration. Patients were included after written informed consent was obtained. No patient refused to give their consent and no patient was lost to the follow-up. The study protocol was approved by the hospital’s Ethics Committee.

Procedure

Antiarrhythmic drug therapy was stopped at least five half-lives before the ablation, except in patients receiving amiodarone. Patients on oral anticoagulation stopped medication 3 days prior to the procedure and low-molecular-weight heparin was administered until the day before ablation. Patients underwent transoesophageal echocardiography prior to the ablation.

Catheters were introduced percutaneously through the femoral vein and a transseptal puncture was performed after verifying the absence of a patent foramen ovale to access the LA. After transseptal access, a bolus of intravenous heparin (5000 IU) was administered, with an additional bolus to maintain an activated clotting time of more than 200 s. The ablation procedure was performed under deep sedation.

All the patients underwent CPVA in order to achieve voltage abatement of the electrograms of the encircled areas, as previously described. A three-dimensional map was constructed using an electroanatomical mapping system (CARTO, Biosense-Webster) to support the creation and validation of RF lesions. A thermocouple-equipped 8 mm or irrigated tip catheter (Navistar, Biosense-Webster) was used. Target temperature was 55°C at a maximum output of 60 W for the 8 mm tip catheter and 45°C at a maximum output of 40 W for the irrigated tip catheter.

The ablation scheme consisted of lesions that encircled both left- and right-sided PVs in order to achieve a local electrogram < 0.15 mV within this area. Supplementary linear lesions along the LA posterior wall and roof and along mitral isthmus were deployed. Finally, electrical disappearance/reduction was checked by mapping the encircled area (Figure 1).

Long-term follow-up

All included patients were followed up for at least 6 months. Follow-up consisted of outpatient visits and 24 h Holter monitoring at 1, 4, and 7 months, and every 6 months thereafter if the patient remained asymptomatic. Patients were also asked to report any symptoms of arrhythmia between scheduled visits. A transthoracic echocardiogram and a magnetic resonance angiography were routinely performed 4 months after ablation. All patients continued oral anticoagulation to maintain an international normalized ratio of between 2.0 and 3.0 for a minimum of 2 months. Previous antiarrhythmic therapy was maintained for at least 1 month and then discontinued if there were no recurrences 1-3 months after ablation.

Symptomatic or asymptomatic AF episodes presenting after the first month were considered as a recurrence.

Statistical analysis

The relationship between baseline clinical and echocardiographic characteristics and the time to recurrence during follow-up was evaluated using survival analysis methodology (Cox regression models). Variables were included in the multivariable analysis using a forward stepwise procedure with a criteria of \( P < 0.05 \) for inclusion and \( P > 0.10 \) for removal from the model.

Validation of the proportional hazard assumption for the final multivariable model was made through a graphical examination of log minus log plots of the Kaplan-Meier survival curves vs. the log of time.

The multivariable model was validated by bootstrap bagging with 1000 samples. In the bootstrap procedure, repeated samples of the same number of observations as the original database were randomly selected with replacement from the original set observations. For each sample, stepwise regression analysis was performed. The stability of the final stepwise model can be assessed by identifying the variables that enter most frequently in the repeated bootstrap models and comparing those variables with the variables in the final stepwise model. If the final stepwise model variables occur in >50%

Figure 1 (A) The ablation scheme performed in all patients and (B) checking of low voltage inside the encircled area after the procedure.
of the bootstrap models, the original final stepwise regression model was judged as stable.

A two-sided $P$-value $\leq 0.05$ was considered statistically significant. The analyses were performed using the SPSS 11.0 (SPSS, Chicago, IL, USA) and Stata 9 (Stata Corp., College Station, TX, USA) statistical packages.

Results
Patient characteristics and results
A group of 148 consecutive patients were included in the study. A second procedure was performed in 22 (14.8%) patients because of recurrent AF (8 patients, 5.4%) or left atrial flutter (14 patients, 9.5%), and a third procedure was necessary in four of those patients (2.7%). Structural heart disease was present in 19.6% of patients and hypertension in 33.8%, and AF was persistent or permanent in 39.2% of the study population. Baseline clinical and echocardiographic pre-procedural characteristics are depicted in Table 1.

After a mean follow-up of $13.1 \pm 8.4$ months, 73.6% of patients in the whole group were free of AF recurrences.

Complications
Two (1.3%) patients suffered a transient cerebrovascular ischaemia. Six (4%) patients had post-procedural pericarditis, and two of them (1.3%) developed a Dressler syndrome. Cardiac tamponade occurred in three (2%) patients, two during transseptal puncture (resolved by pericardiocentesis) and one during ablation (resolved by surgery). Magnetic resonance angiography was performed in all patients prior to and 4 months after CPVA and did not reveal any stenosis of the pulmonary veins.

After the first procedure, 16 patients presented LA flutter, 14 underwent a second procedure, and 2 patients were treated with electrical cardioversion. After a second procedure, only three (2%) patients presented recurrent LA flutter (one post-CPVA relapse and two post-electrical cardioversion); one was resolved through a third procedure and the other with antiarrhythmics and cardioversion.

Univariable analysis
Table 2 shows the univariable analysis of pre-procedural variables and the risk of AF recurrence. It should be noted that the risk of AF recurrence increases with age (HR 1.03; 95% CI 1.00–1.06, $P = 0.031$), with the presence of previous hypertension (HR 2.7; 95% CI 1.43–5.07, $P = 0.002$), and when AF is permanent (HR 2.23; 95% CI 1.08–4.59, $P = 0.042$). Furthermore, larger LAD (HR 1.11; 95% CI 1.05–1.18, $P = 0.001$) and larger left ventricular end-systolic diameter (LVEDD) (HR 1.07; 95% CI 1.00–1.15, $P = 0.029$) prior to the procedure were associated with AF recurrence after CPVA.

Multivariable analysis
Cox regression analysis showed that the presence of previous hypertension (OR = 2.8; 95% CI 1.5–5.4, $P = 0.002$) and of an enlarged LAD (OR = 1.1; 95% CI 1.06–1.2, $P = 0.001$) was an independent predictor of AF recurrence after CPVA (Table 3).

The log minus log plots of the Kaplan–Meier survival curves vs. the log of time showed approximately parallel straight lines, indicating that the proportional hazard assumption was reasonable.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients included in the study</th>
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<tbody>
<tr>
<td>Characteristics of patients</td>
<td></td>
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<tr>
<td>Patents</td>
<td>148</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$52 \pm 11$</td>
</tr>
<tr>
<td>Male gender</td>
<td>122 (82.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (33.8)</td>
</tr>
<tr>
<td>Type of AF</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>90 (60.8)</td>
</tr>
<tr>
<td>Persistent</td>
<td>35 (23.6)</td>
</tr>
<tr>
<td>Permanent</td>
<td>23 (15.5)</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>29 (19.6)</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>$74.6 \pm 68.4$</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>LAD (mm)</td>
<td>$41.4 \pm 5.6$</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>$51.3 \pm 5.3$</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>$32.7 \pm 5.1$</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>$10.6 \pm 1.5$</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>$10.1 \pm 1.1$</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>$60 \pm 10.9$</td>
</tr>
</tbody>
</table>

Data are expressed as mean $\pm$ SD or number (%). AF, atrial fibrillation; LAD, anteroposterior left atrial diameter; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVEF, left ventricular ejection fraction.

<table>
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<tr>
<th>Table 2</th>
<th>Univariable analysis of pre-procedural variables and the risk of AF recurrence</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00–1.06)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.02 (0.45–2.32)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.70 (1.43–5.07)</td>
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<tr>
<td>Permanent AF</td>
<td>2.23 (1.08–4.59)</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>1.28 (0.61–2.69)</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>1.11 (1.05–1.18)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>1.05 (0.98–1.12)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>1.07 (1.00–1.15)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.98 (0.95–1.01)</td>
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<tr>
<td>IVS (mm)</td>
<td>0.99 (0.78–1.27)</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>1.05 (0.74–1.48)</td>
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LVEDD, left ventricular end-systolic diameter.

* $P < 0.05$.

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<tr>
<th>Table 3</th>
<th>Multivariable analysis</th>
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<tbody>
<tr>
<td>Variable</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>LAD</td>
<td>1.1 (1.06–1.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.8 (1.5–5.4)</td>
</tr>
</tbody>
</table>

Independent pre-procedural predictors of AF recurrence after ablation procedure.
Bootstrap validation of the multivariable model showed that hypertension and LAD variables entered in 90 and 80% of the analyses, respectively. Moreover, estimated model (only hypertension and LAD as independent predictors) was observed in 54% of the bootstrapped samples; additionally, in 19% of the models, these two variables appeared with another variable and only in 3% of them, they did not appear simultaneously.

Predicted model for atrial fibrillation recurrence

The mean predicted proportion of patients with AF recurrences after CPVA of the multivariable model showed a linear relationship with the increase in LAD prior to the procedure. In addition, the presence of hypertension further increased the mean predicted proportion of patients with AF recurrences at each LAD (Figure 2).

Given these data, it is possible to identify four subgroups of patients with different probabilities of AF recurrence (Figure 3). The subgroup of patients with an LAD ≤45 mm and without hypertension has a probability of >85% of maintaining long-term sinus rhythm after CPVA. In contrast, the subgroup of patients with hypertension and an LAD >45 mm have a probability of maintaining sinus rhythm after CPVA of ~50%.

Discussion

Previous reports have demonstrated that LAD is a predictor of recurrences after cardioversion or mini-maze procedure. Thus, it is not surprising that LAD prior to CPVA was shown to be a stronger independent predictor of AF recurrences. The major contribution of this study is the demonstration of a linear relationship between the increase of LAD and the mean predicted proportion of patients with AF recurrence after CPVA, and the additional increase of this proportion in the presence of hypertension. Up to now, pre-procedural independent predictors of AF recurrence have not been described for CPVA, probably because most reports included a relatively small number of patients or multivariable analyses either were not performed or may not have had sufficient power to identify them.

As far as we have known, only the age >50 years and the presence of persistent vs. paroxysmal AF have been identified as independent pre-procedural predictors of AF recurrences after AF ablation, but only for segmental ostial ablation. In the present study, the univariable analysis shows that the risk for AF recurrence increases with age, with the presence of previous hypertension, when AF is permanent, and with the increase of LAD and LVESD (significant statistical association). However, the multivariable analysis shows that the only independent predictors of AF recurrence are LAD and the presence of previous hypertension, thus suggesting that permanent AF is associated with more powerful predictors of recurrences, i.e. enlarged LAD.

The results of the present study are consistent with the published data as regards the efficacy of CPVA. It has recently been reported that CPVA may achieve restoration of sinus rhythm in chronic AF and even in prosthetic heart valve patients. The success rate achieved in these circumstances (74 and 73%, respectively) was lower than that for paroxysmal AF (85%) reported by the same investigators. It is noteworthy that the mean LAD in a case of chronic AF or a prosthetic heart valve patient (45 ± 6 and 55 ± 5 mm, respectively) was larger than in paroxysmal AF patients (<40 mm), thus illustrating that the more dilated the atria the lower the success rate.

The finding that hypertension is a risk factor for AF recurrence after CPVA is consistent with the literature. Hypertension is the most prevalent risk factor for AF, with a relative risk of ~1.2 in the general population. However, it is also a modifiable cause of left atrial enlargement and fibrosis, which both contribute to the development of AF. The fact that a history of hypertension acts as an independent predictor of AF after CPVA, with a relative risk of 2.8, suggests two explanations for its negative effect: hypertensive patients might have more diseased atria for the same LAD or, alternatively, there is poor control of hypertension after the procedure. We could assume that LAD enlargement is a
surrogate measure of chronic elevation of left ventricular filling pressures as a consequence of poor diastolic function in hypertensive patients. 19-21

Although patients with AF recurrences were more likely to suffer from hypertension, there were no differences between patients with or without AF recurrences, with respect to the thickness of the septum and the posterior wall of the left ventricle (Table 2). However, the lack of difference in wall thickness suggests that more subtle changes, probably at the atrial level, occur in patients with hypertension, even before changes in the thickness of the left ventricular wall develop.

Clinical implications

The identification of strong predictors of AF recurrences (i.e. hypertension) and the linear relationship between LAD and the mean predicted proportion of patients maintaining sinus rhythm after CPVA makes it possible to identify patients with different long-term success probabilities. This stratification may help to select patients to undergo the procedure and to inform them about the risk–benefit ratio. Given the present results, it may be acceptable to start performing CPVA for ablation of symptomatic recurrent AF as an intervention of choice in the subgroup with a greater probability of success.

The results also highlight the need for aggressive treatment of hypertension to prevent AF, because the probability of restoring long-term sinus rhythm after AF ablation is smaller in these patients. In addition, it is not known whether certain antihypertensive drugs or well-controlled arterial pressure after CPVA may reduce AF recurrences, as has been demonstrated in primary and secondary prevention trials of AF. 22,23 Further studies are needed to clarify these points.

Study limitations

It is not possible for us to know the number of patients initially assessed for inclusion into the study because our institution is a reference centre and we ignore the number of screened patients. Thus, we do not know the proportion of ineligible AF patients for AF ablation, although the inclusion criteria are not highly restrictive.

Although variables like structural heart disease vs. normal heart did not show any predictive value for recurrence, it is possible that these conditions are underrepresented in this study population. Therefore, it is likely that they are also important factors to be taken into account. However, we have analysed only the most well-known clinical and echocardiographic predictors of new onset AF, 18 or recurrent episodes after conversion to sinus rhythm. 13 Although other clinical variables may predict AF recurrence, the present results suggest that it would be appropriate to stratify the probability of success by means of these two simple variables.

Conclusions

Hypertension and LAD are strong predictors of AF recurrence after CPVA and may be useful in selecting the best candidates in whom to perform the procedure.

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Conflict of interest: none declared.

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