LEFT ATRIAL POSTERIOR WALL ISOLATION DOES NOT IMPROVE THE OUTCOME OF CIRCUMFERENTIAL PULMONARY VEIN ABLATION FOR ATRIAL FIBRILLATION: A PROSPECTIVE RANDOMIZED STUDY

David Tamborero, B.Eng., Lluís Mont, M.D., Ph.D., Antonio Berruezo, M.D., Maria Matiello, M.D., Begoña Benito, M.D., Marta Sitges, M.D., Ph.D., Barbara Vidal, M.D., Teresa M de Caralt, M.D., Ph.D., Rosario J Perea, M.D., Radu Vatasescu M.D., and Josep Brugada, M.D., Ph.D.

Arrhythmia Section, Thorax Institute
Hospital Clinic, University of Barcelona, Catalonia, Spain.

Short title: Isolation of the LA posterior wall in AF ablation

Total word count: 4661

Subject code: [22]

Address for correspondence:
Dr. Lluís Mont
Cardiovascular Institute
Hospital Clínic Universitari de Barcelona
Villarroel 170
08036 Barcelona
Catalonia, Spain
Tel. 00 34 932275551; Fax: 00 34 934513045
E-mail: lmont@clinic.ub.es
BACKGROUND

Ablation of the pulmonary veins (PVs) for atrial fibrillation (AF) treatment is often combined with linear radiofrequency lesions along the left atrium (LA) to improve the success rate. The study was designed to assess the contribution of LA posterior wall isolation to the outcome of circumferential pulmonary vein ablation (CPVA).

METHODS and RESULTS

CPVA consisted of continuous radiofrequency lesions encircling both ipsilateral PVs plus an ablation line along the mitral isthmus. Patients were then randomized into two groups. In the first group, superior PVs were connected by linear lesions along the LA roof (CPVA-1 group). In the other group, the LA posterior wall was isolated by adding a second line connecting the inferior aspect of the two inferior PVs (CPVA-2 group). The study included 120 patients (53±11 years, 77% male, 60% paroxysmal AF, LA of 41.3±5.4 mm, 46% with hypertension and 22% with structural heart disease).

After a single ablation procedure and a mean follow-up of 10±4 months, 24 (40%) patients of the CPVA-1 group had AF recurrences and 3 (5%) had new-onset LA flutter. In the CPVA-2 group, recurrences were due to AF episodes in 23 patients (38%) and LA flutter in 4 (7%). Freedom from arrhythmia recurrences was not statistically different in CPVA-1 group as compared to CPVA-2 (log rank p=0.943).

CONCLUSION

Isolation of the LA posterior wall did not increase the success rate of CPVA.

Key words: Arrhythmia, catheter ablation, atrium
INTRODUCTION

Since the initial description of paroxysmal atrial fibrillation (AF) triggered by pulmonary vein (PV) firing\(^1\), several approaches to catheter ablation have been developed to treat AF. At present, PV isolation is performed in almost all AF ablation procedures\(^2\)\(^-\)\(^4\). Deployment of linear lesions along the left atrium (LA) in addition to PV ablation has been shown to improve the success rate\(^5\)\(^-\)\(^7\). The most commonly performed procedure involves ablation of the mitral isthmus and connection of the superior contralateral PVs through the LA roof\(^8\)\(^,\)\(^9\). Other authors have suggested a lesion set in which the LA posterior wall is also excluded by connecting superior and inferior contralateral PVs along two ablation lines\(^6\)\(^,\)\(^10\)\(^-\)\(^12\). However, there are no data comparing the two approaches.

The aim of this prospective randomized study was to evaluate whether isolation of the LA posterior wall decreased arrhythmia recurrence risk after circumferential pulmonary vein ablation (CPVA).

METHODS

The study included 120 consecutive patients undergoing a first catheter ablation for symptomatic, drug-refractory (≥2 antiarrhythmics) AF, classified as paroxysmal, persistent or long-standing, according to HRS/EHRA/ECAS consensus\(^13\). No patient refused to give consent and no patient was lost to follow-up. The study protocol was approved by the hospital’s Ethics Committee. The authors take responsibility for the integrity of the data. All the authors have read and agree to the manuscript as written.

All patients underwent transesophageal echocardiography 1 to 5 days before ablation to exclude the presence of intracavitary thrombus. A transthoracic
echocardiogram and a gadolinium-enhanced magnetic resonance angiogram (MRA) were also obtained before the procedure.

After trans-septal access, a bolus of intravenous heparin (5000 IU) was administered, with an additional bolus to maintain an activated clotting time of more than 250 s. The procedure was performed under deep sedation. Ablation was assisted by a three-dimensional map of the LA and its adjacent structures, produced with CARTO (Biosense Webster) or NavX (St Jude Medical) systems. MRA images were integrated into the navigation system to support the LA anatomical reconstruction. Radiofrequency was delivered by a thermocouple-equipped 3.5 mm cooled-tip catheter at a target temperature of 48º C and a maximum output of 40 W.

Patients were randomized into two ablation groups. In both, continuous radiofrequency lesions surrounding each ipsilateral PV antrum were deployed until the local electrogram inside the encircled area disappeared or was dissociated or, when this was not possible, until the bipolar voltage amplitude dropped to <0.15 mV; electrical block was confirmed by the inability to conduct to the LA after pacing at several sites within the PV antrum. PV antrum was defined as the anatomical transition between LA and PV structures and was mainly identified by three-dimensional reconstruction. Mitral isthmus ablation was also performed in all patients by creating a radiofrequency line from the inferior-lateral aspect of the left PV lesions to the mitral annulus. Then, in the first group (CPVA-1), a radiofrequency line was created connecting contralateral PV-encircling lesions through the LA roof. In the second group (CPVA-2), the LA posterior wall was excluded by adding a second ablation line connecting the inferior aspect of the two inferior PVs. In both groups, separated local double potentials or potential disappearance all along the LA roof ablation line was used as the criterion to define electrical block. In the CPVA-2 group, after completion of the roof line, the
infero-posterior line was deployed until the absence or dissociation of local electrogram inside the excluded LA posterior region was observed; isolation was confirmed by the inability to conduct to the remaining atria after pacing at several sites within the surrounded LA posterior region with the ablation catheter, observing the local capture in the proximal bipole of the pacing catheter when possible. Each end-point of the ablation procedure was assessed in sinus rhythm, performing electrical cardioversion if necessary.

Follow-up

Patients were followed up at the outpatient clinic at 1, 4 and 7 months after the ablation procedure and every 6 months thereafter if they remained asymptomatic. Routine 48-h Holter monitoring was performed before each visit. Patients were also asked to come to the emergency department if any symptom suggestive of recurrence occurred between scheduled visits. All patients continued oral anticoagulation to maintain an international normalized ratio between 2.0 and 3.0 for a minimum of two months after ablation. All patients received antiarrhythmic medication for a minimum of 1 month after the procedure to decrease early recurrences (flecainide if no structural heart disease was diagnosed or amiodarone if there was evidence of structural heart disease). Ablation was considered successful in those patients with no AF recurrences or LA flutter after a blanking period of 3 months. Minimum follow-up of this series was 6 months.

Statistical analysis

The primary end-point of the study was freedom from arrhythmia recurrence after a single ablation procedure. Based on our own experience, at 6 months follow-up
55% of patients were expected to be free of arrhythmia after a single CPVA-2 procedure. With a sample size of 60 patients per arm, a log-rank test for equality of survival curves will have 80% power and a two-sided alpha value of 0.05 to detect an expected 20% reduction in freedom from arrhythmia in the CPVA-1 group. Subjects were included during the first 18 months of the 24-month study, with no loss to follow-up expected.

Randomization was performed according to a computer-generated algorithm in blocks of 20 patients. The ablation group was blinded to patients and to the physicians evaluating the outcome of the procedure.

Data are reported as mean ± SD. Comparisons between groups were performed using Student’s t test or Chi-square analysis. Arrhythmia-free survival curves for each group were presented as Kaplan-Meier plots and compared by log-rank test.

Cox method was used to estimate the effect of LA posterior wall isolation after adjusting for baseline variables. The following potential predictors of recurrence were considered: age, sex, type and duration of AF, LA diameter, left ventricular end-diastolic and end-systolic diameters, left ventricular ejection fraction, hypertension and structural heart disease. Stepwise method with criteria of $p \leq 0.05$ for inclusion and $p \geq 0.10$ for removal was used to select the covariates and report the estimates from the model that included those covariates and the variable isolation (or not) of the LA posterior wall.

A two-sided $p$ value $\leq 0.05$ was considered statistically significant. Analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, Illinois) and Stata 9 (Stata Corp., College Station, TX) statistical packages.

RESULTS
The study included 120 consecutive patients; baseline characteristics are shown in Table 1. No significant baseline differences were observed between the groups. Procedure details are given in Table 2. End-points of the procedure were confirmed using previously described criteria in 54 and 55 patients of the CPVA-1 and CPVA-2 groups, respectively (90% vs. 92%; p=0.75).

After a mean follow-up of 9.8±4.3 months, 33 patients (55%) in both groups had no arrhythmia recurrences after a single ablation procedure (log-rank test p=0.943). The success rate was higher in paroxysmal AF than in persistent/long-standing AF, but no statistical differences were observed in arrhythmia recurrences between those with or without LA posterior wall isolation (Figure 2). Among patients with no recurrences, 28 CPVA-1 and 27 CPVA-2 patients (47% and 45%, respectively) were not treated with antiarrhythmics (log rank test p=0.908), and 5 CPVA-1 and 6 CPVA-2 patients were taking one antiarrhythmic drug: in 3 and 4 patients, respectively, the antiarrhythmic was not withdrawn during the blanking period due to early recurrences, but they had no arrhythmias after the three-month blanking period, and 2 patients of each group took flecainide due to symptomatic premature atrial beats, but they had no sustained episodes.

In the CPVA-1 group, recurrences were due to AF episodes in 24 patients (40%) and to LA flutter in 3 (5%). In the CPVA-2 group, 23 patients (38%) had AF recurrences and 4 (7%) had new-onset LA flutter.

Cox regression indicated that the baseline LA diameter was the only covariate significantly associated with arrhythmia recurrence (HR =1.078 (95% CI: 1.011-1.148); p=0.021). The adjusted HR obtained for the variable isolation of the LA posterior wall
was consistent with the log rank test result (HR =0.893 (95% CI: 0.581-1.549); p=0.722).

**Complications**

There were no differences between the groups in the number of procedural complications (Table 2). Two CPVA-1 patients and 1 CPVA-2 patient suffered a transient cerebrovascular ischemia, which was resolved under heparin with normal computed tomography scanning. One patient in each group showed transient inferior myocardial ischemia, probably related to catheter manipulation during trans-septal catheterization due to air embolism; the ischemia was resolved with sublingual NTG within a few minutes, without consequences.

In addition, 1 CPVA-1 and 2 CPVA-2 patients had post-procedural pericarditis that required non-steroidal anti-inflammatory treatment. Magnetic resonance angiogram performed prior to and 4 months after ablation in all patients of this series did not reveal any severe (>70%) PV stenosis; one patient of the CPVA-2 group showed a left superior PV narrowing of 55%.

**Second ablation procedures**

The ablation procedure was repeated in 25 (20.8%) patients. Overall, after a mean of 1.2±0.4 ablation procedures, 67.7% of the patients of this series remained arrhythmia-free.

In 4 patients, the ablation was repeated due to new-onset LA flutter. In all 4 cases, an activation map produced by the navigation system plus entrainment maneuvers showed that the re-entry was established between gaps of the previous right-sided or left-sided encircling lesions.
In the remaining 21 patients, the second procedure was performed due to AF recurrences. The previous ablation set was evaluated and radiofrequency was delivered in sites showing conduction gaps. Recurrent electrical conduction in a mean of 3.1±0.9 PV per patient was found in 17 of the 21 patients (84%), whereas all PV remained isolated in 4 patients. Conduction across the LA roof line and electrical activity within the LA posterior wall was observed in 69% and 67% of the CPVA-1 and CPVA-2 patients, respectively. In one CPVA-2 patient, extensive fibrosis was observed along both atria, without electrical activity in the previously isolated areas; no further ablation was performed and it was decided to leave the patient in permanent AF.

DISCUSSION

The main finding of this study is that electrical isolation of the LA posterior wall did not increase the success of CPVA. Deployment of linear lesions along the LA roof, mitral isthmus or both locations has been shown to improve the outcome of PV ablation. Moreover, some authors advocate a lesion set in which the LA posterior wall is also excluded by connecting the superior and inferior contralateral PVs through both ablation lines. However, the number and location of linear lesions that will obtain the best results has not been well established. Several surgical methods were originally used to treat AF with a predefined set of linear lesions, based on the multiple wavelet hypothesis and the idea that sustained AF requires a critical amount of contiguous atrial tissue. At present, the main mechanism leading to AF is not clearly defined. PV firing has been considered as a main trigger of paroxysmal AF, and larger LA regions may act as the AF substrate in more persistent AF. In this regard, extensive LA ablation has been included in many of the current AF catheter procedures.
The role of the LA posterior wall in triggering and driving fibrillation has been suggested by both human and animal studies. However, in the present series, exclusion of the LA posterior wall had no effect on the incidence of AF recurrences after CPVA. It should be noted that a larger area of posterior venous-atrial tissue was excluded when PV encirclement was performed in this study as compared to procedures in which PVs are ablated at their ostia. A recent study suggested that large PV ablation circles increase the success rate of the procedure. It is thus possible that the AF substrate of the LA posterior wall is mainly located within the lesions around the PV antrum and no further ablation is required.

Our results also showed no difference between the CPVA-1 and CPVA-2 groups in terms of the risk of LA flutter. The incidence of new-onset LA flutter has been described after AF ablation procedures, in which gaps along large lesions may create an ideal substrate for re-entrant circuits. Pappone et al. demonstrated that mitral isthmus ablation plus the addition of two posterior linear lesions reduced the risk of developing this arrhythmia after CPVA. In the present study, the deployment of two ablation lines connecting left and right sided PVs showed no benefit in preventing LA flutter, compared to creating a single roof line. In all procedures performed to treat LA flutter after the index ablation, a re-entrant circuit through gaps in the prior PV-encircling lesions was observed, in accordance with other series. It is known that the continuity of linear lesions around ipsilateral PVs is difficult to achieve, especially at the PV septal aspect and the region between the LA appendage and the left superior PV.

To our knowledge, this is the first study to demonstrate that the performance of LA posterior wall isolation does not improve the outcome of CPVA. Although the total time of radiofrequency delivery did not increase significantly when the ablation line was added along the LA posterior-inferior wall, there is a major potential risk of lesion to
the esophagus, since it is virtually in contact with this region. Moreover, isolation of the posterior LA region could theoretically impair atrial function. Therefore, according to the results of this study, we conclude that the electrical exclusion of the LA posterior wall is not necessary when performing CPVA as a predefined lesion set to treat AF.

Study limitations

The study was planned to detect an absolute reduction of 20% in the proportion of freedom from arrhythmia. However, the same number of patients was arrhythmia-free in both groups, and consequently, the result from the formal comparison is far from the 5% significance level and the adjusted hazard ratio for arrhythmia recurrence was close to 1. Therefore, the lack of statistical significance may not be attributable to low statistical power.

The effect of LA posterior wall isolation was evaluated as part of a predefined lesion set performed in all patients. Therefore, the study cannot exclude that the isolation of the LA posterior wall may have some effect in individual AF cases. Recently, individualized approaches for AF ablation have been proposed, but the criteria to pre-select the ablation method in each patient or the end-point for a tailored procedure are still under investigation.

Mitral isthmus ablation was performed anatomically without demonstrating electrical block. This may theoretically create a pro-arrhythmic substrate due to the effect of incomplete linear lesions, although no peri-mitral re-entry was observed in any patient submitted to a second procedure. Additionally, PV isolation was not assessed by circular catheter mapping, as originally described by Haissaguerre et al. In any case, ablation technique was the same in both groups except for the performance of the infero-posterior ablation line, and probably did not affect the conclusions of the study.
Because no additional catheter was placed at the LA, the achievement of local capture during pacing maneuvers was often difficult to demonstrate since it was assessed by the proximal pair recording of the ablation catheter\textsuperscript{10} (while pacing through the distal). However, in these cases, the absence of local electrogram or dissociation from the remaining atria should be a reasonable surrogate marker of the LA posterior wall isolation\textsuperscript{6}.

Finally, with the available follow-up limited to routine 48h-Holter monitoring and ECG recording when symptoms occurred between scheduled visits, arrhythmia recurrences may have escaped detection in asymptomatic patients. However, this was a pragmatic approach that obtained a reasonable follow-up in light of other published studies\textsuperscript{5,7,10,33,41-44}; moreover, this limitation should have occurred equally in both ablation groups and therefore would not affect the conclusions of the study.

**CONCLUSION**

Isolation of the LA posterior wall did not offer additional benefit over a single roof line lesion with respect to the risk of arrhythmia recurrence after CPVA.
FUNDING SOURCES

D Tamborero was supported by a grant from Institut de Investigació Biomèdica August Pi i Sunyer (IDIBAPS).

DISCLOSURES

No conflicts of interest are stated.

ACKNOWLEDGEMENTS

The authors thank Albert Cobos, M.Sc., Ph.D., for statistical support and Elaine Lilly, Ph.D., for manuscript editing.
References


**Figure Legends.**

**Figure 1.** Anatomical reconstruction of the LA showing ablation scheme of CPVA-1 (left panel) and CPVA-2 (right panel) groups. Red dots represent sites of radiofrequency delivery.

LA: left atrium; PV: pulmonary vein; LAA: LA appendage; LSPV: Left superior PV; LIPV: Left inferior PV; RSPV: Right superior PV; RIPV: Right inferior PV.

**Figure 2.** Accumulated arrhythmia recurrence survival after a single ablation procedure in: (A) whole series, (B) subgroup of paroxysmal AF patients, (C) subgroup of persistent or long-lasting AF patients. Solid and dotted lines represent CPVA-1 and CPVA-2 groups, respectively.
<table>
<thead>
<tr>
<th></th>
<th>CPVA-1 group</th>
<th>CPVA-2 group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><strong>Type of AF</strong></td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>37 (62%)</td>
<td>35 (58%)</td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>11 (18%)</td>
<td>13 (22%)</td>
<td></td>
</tr>
<tr>
<td>Long-standing AF</td>
<td>12 (20%)</td>
<td>12 (20%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.5±10.9</td>
<td>52.9±10.8</td>
<td>0.83</td>
</tr>
<tr>
<td>Male sex</td>
<td>44 (73%)</td>
<td>48 (80%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of AF (months)</td>
<td>60.8±55.7</td>
<td>67.1±48.2</td>
<td>0.58</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>41.1±5.0</td>
<td>41.6±5.9</td>
<td>0.65</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>52.7±4.1</td>
<td>52.5±5.4</td>
<td>0.80</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>32.8±4.8</td>
<td>34.4±7.1</td>
<td>0.25</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>59.8±9.8</td>
<td>59.5±10.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (43%)</td>
<td>29 (48%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>13 (22%)</td>
<td>13 (22%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; LA: left atrial; LV: left ventricular.

Data are expressed as mean±SD when appropriate.
Table 2
Procedural details

<table>
<thead>
<tr>
<th></th>
<th>CPVA-1 group</th>
<th>CPVA-2 group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>114.3±23.4</td>
<td>120.9±37.7</td>
<td>0.10</td>
</tr>
<tr>
<td>Fluoroscopic time (min)</td>
<td>23.2±7.8</td>
<td>22.6±8.3</td>
<td>0.60</td>
</tr>
<tr>
<td>RF time (min)</td>
<td>39.2±7.7</td>
<td>42.5±9.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient cerebrovascular ischemia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transient inferior myocardial ischemia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

RF: radiofrequency.
Data are expressed as mean±SD when appropriate.
Figure 1
Figure 2.