Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison

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Introduction

Since the pioneering work of Haissaguerre et al.1 has identified the pulmonary veins (PV) as the predominant trigger location for paroxysmal atrial fibrillation (AF), pulmonary vein isolation (PVI) using segmental ostial ablation strategies has been introduced in treating paroxysmal AF.2–4 The reported clinical success rates following initial PVI vary around 60–70% depending on the individual definition of success, the intensity of follow-up investigation, and concomitant anti-arrhythmic drug treatment.2–4 However, these encouraging success rates for PVI in paroxysmal AF have not been achieved in the setting of persistent AF, which has been shown to be associated with a significantly higher recurrence rate.3 Linear ablation strategies5,6 have been shown to successfully modify the substrate especially when electrophysiological lesion completeness was achieved.8,9 Left atrial (LA) isthmus ablation between posterior mitral annulus (MA) and left inferior pulmonary vein (LIPV) has been recently introduced as an adjunctive strategy to PVI providing encouraging results for patients with paroxysmal AF.9 Furthermore, additional selective LA isthmus ablation improved the outcome in those patients in whom AF was inducible for more than 10 min after PVI alone.10 Thus, the aim of the present prospective randomized study was to investigate the effectiveness of additional substrate modification (SM) by LA linear lesions in patients with persistent AF.

Aims

To investigate the effectiveness of additional substrate modification (SM) by left atrial (LA) linear lesions as compared with pulmonary vein isolation (PVI) alone in patients with persistent atrial fibrillation (AF) in a prospective randomized study. Percutaneous PVI has evolved as an accepted treatment for paroxysmal AF but seemed to be less effective in patients with persistent AF. The benefit of PVI alone and additional linear lesions has not been validated in a randomized study so far.

Methods and results

Sixty-two patients with persistent AF (median duration 7, range 1–18 months) were randomly assigned to either PVI alone (n = 30) or additional SM (n = 32) consisting of a roof line connecting both left superior and right superior PV and LA isthmus ablation between left inferior PV and mitral annulus. Procedures including SM were performed using a three-dimensional mapping system (EnSite NavX™, St Jude Medical, St Paul, MN, USA). Anti-arrhythmic drugs were discontinued within 8 weeks after ablation in both groups. Follow-up included daily phone ECG irrespective of the patient’s symptoms. PVI was successful in 98% of all targeted veins in both groups. Additional SM did not increase fluoroscopy time (72.1 ± 18.7 vs. 72.9 ± 17.3 min, P = 0.92) because of the use of three-dimensional navigation in the PVI + SM group. AF recurrences within the first 4 weeks following ablation were more common after PVI alone (77%) than additional SM (44%, P = 0.002). After a follow-up time of 487 (429–570) days, only 20% of patients undergoing stand alone PVI remained in sinus rhythm when compared with 69% following PVI combined with SM (P = 0.0001). Two patients assigned to PVI + SM experienced procedure-related complications (cardiac tamponade and minor stroke) which resolved without sequelae.

Conclusion

PVI alone is insufficient in the treatment of persistent AF. However, additional left linear lesions increase the success rate significantly. Early AF-relapses are associated with a negative outcome after PVI alone but not following additional SM.

KEYWORDS

Atrial fibrillation; Catheter ablation; Linear ablation; Mapping

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Methods

Patients

Inclusion criteria
Enrolled patients had to meet the following criteria: (i) at least two failed attempts of an anti-arrhythmic drug therapy for symptomatic AF episodes; (ii) persistent AF lasting for at least 1 month documented by daily trans-telephonic transmitted ECG (Tele-ECG). Patients with concomitant severe heart disease and impaired systolic left ventricular (LV) function (LVEF <40%) and/or LA enlargement more than 55 mm were excluded from the study.

Hypothesis
In the current study we tested the hypothesis that additional SM by LA linear lesions in patients with persistent AF reduces recurrence of AF.

Study size design and primary endpoint
We hypothesized that additional SM reduces symptomatic and asymptomatic recurrences in patients with persistent AF undergoing PVI. A two-sided significance level of 5% was used against an estimated difference between the groups of 25%.

In equivalence testing, a number of at least 47 patients in each group was mandatory. Considering a potential drop out of 5%, a total study cohort of 100 patients was calculated. Primary endpoint of the study was recurrence of symptomatic AF or the documentation of AF episodes >30 s by Tele-ECG apart from those episodes exclusively occurring within the first 4 weeks after RFC ablation. Patients were either randomized for PVI alone, including right atrial isthmus ablation or for additional ablation at the roof and the LA isthmus. Baseline characteristics demonstrated in Table 1 did not differ significantly between both groups.

Randomization
All consenting patients were enrolled and randomized into the trial by allocating them to one of the two arms (see patient flow diagram). The randomization sequence was generated by a random number table.

Interim analysis
The patient enrolment will be stopped if PVI + SM is superior to PVI alone or the sample size will be adjusted if the observed event rates are different from the assumptions of the fixed study design. An interim analysis was planned and performed after completing 6 months follow-up of 50 patients using the O’Brien and Flemings design for alpha spending (ADDPLAN 3.0.1). At that time, an overall number of 62 patients (n = 30 PVI alone, n = 32 PVI + SM) was included into the study. After the interim analysis, the trial was prematurely stopped.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>PVI + SM</th>
<th>PVI alone</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.3 ± 11.8</td>
<td>60.1 ± 9.3</td>
<td>0.47</td>
</tr>
<tr>
<td>Median duration of current AF (months)</td>
<td>7 (1–18)</td>
<td>7 (2–17)</td>
<td>0.54</td>
</tr>
<tr>
<td>No. of ineffective AA agents (median)</td>
<td>3 (2–7)</td>
<td>3 (2–7)</td>
<td>0.88</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>47 ± 6</td>
<td>48 ± 4</td>
<td>0.89</td>
</tr>
<tr>
<td>Heart disease– hypertension</td>
<td>n = 12</td>
<td>n = 11</td>
<td>0.89</td>
</tr>
<tr>
<td>CAD</td>
<td>n = 4</td>
<td>n = 4</td>
<td>0.84</td>
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</table>

AA, anti-arrhythmic; LA, left atrium.

Statistical analysis
Data analysis was carried out according to a pre-established analysis plan. Proportions were compared by two-sided binominal-tests using a statistical software (SPSS Inc., Cary, NC, USA). A Kaplan–Meier analysis with the log-rank test was used to determine the probability of freedom of AF recurrence in both groups. P-value <0.05 indicated statistical significance.

ECG monitoring
Each patient received a Tele-ECG recorder (RhythmCard™, Intromedix Inc., San Diego, CA, USA) that could record an ECG for a 1-min duration. Every patient was advised to record and transmit at least one ECG per day irrespective of the individual symptoms as well as one ECG in case of any symptoms. This included a period of 4 weeks before ablation and the complete follow-up time after ablation. ECGs were transmitted to a central laboratory using a regular telephone and a correlation between symptoms and transmitted ECG could be obtained.

Electrophysiological study
Patients were on oral anticoagulation (target range 2–3 INR) for at least 1 month prior to the ablation procedure. The day before the ablation procedure, cardiac-MRI and transoesophageal echocardiograms for exclusion of atrial thrombus were performed. The study was approved by the Institutional Ethics Committee. After written informed consent was obtained, patients underwent electrophysiological study under sedation with propofol during continuous monitoring of blood pressure and saturation. Intracardiac electrograms were filtered from 30 to 250 Hz and stored using a computer-based mapping system (LabSystem™ Pro, BARD Electrophysiology, Murray Hill, NJ, USA). The procedure was performed following the discontinuation of anti-arrhythmic drug treatment for at least four half-lives with the exception of amiodarone. Standard electrode catheters were placed in the high right atrium and coronary sinus (CS). Following transeptal puncture, two steerable catheters were positioned in the LA under the guidance of transseptal sheaths (Preface™ Multipurpose, Biosense Webster Inc., Diamond Hill, NJ, USA).
Substrate modification combined with PVI improves outcome of catheter ablation in patients with persistent AF

Bar, CA, USA: an irrigated-tip ablation catheter (Celsius ThermoCool™, Biosense Webster Inc., Diamond Bar, CA, USA) and a circular mapping catheter equipped with 10 1-mm-electrodes (Lasso™, Biosense Webster Inc., Diamond Bar, USA) which was placed in an ostial position of the PVs. Prior to the ablation, selective angiography of all accessible veins was performed by injection of 5–10 mL contrast medium via the sheath or using a diagnostic catheter (NIH, Cordis, Miami Lakes, FL, USA). Continued anticoagulation was initiated by application of 50 IU/kg heparin and adjusted as required in order to maintain the activated clotting time (ACT) between 250 and 300 s.

**EnSite NavX™-system**

Technical details of this non-fluoroscopic navigation system integrated as a part of the EnSite system have been described previously. Briefly, all conventional electrodes can be visualized within the electric field generated via six electrodes that constitute three orthogonal axes with the heart in their centre. A 5.68 kHz constant low-current locator signal is multiplexed with each pair of surface electrodes to create a transthoracic electrical field. The potential difference between these electrode pairs and each catheter electrode is measured. Any movement of the catheter electrodes results in a change of measured voltage and impedance of each electrode. The position in space of each electrode can be determined with the accuracy of 0.6 mm for a wide range of patient body masses. To obtain three-dimensional intra-cardiac geometry, a conventional mapping catheter is swept throughout the hearts cavity, defining endocardial boundaries. Characteristic anatomic landmarks or ablation sites can be tagged and a shadow can be displayed on each catheter to record the respective spatial position.

**Pulmonary vein isolation**

In both groups circumferential PV mapping using the Lasso™ catheter placed at an ostial position guided ablation. Initially, cardioversion was performed in both groups in order to have similar conditions during ablation and to avoid a shift of the three-dimensional mapping image in the PVI + SM group because of potential interference with direct current delivery. Initially, the posterior wall of each vein was targeted and the ablation line was deployed 1 cm proximally from the ostial region labelled by the Lasso™ catheter as previously described by Haissaguerre et al. Ablation started at the left superior PV and was continued around the entire vein including the anterior aspect as required to achieve complete electrical disconnection. RF was applied using an open irrigated-tip catheter with a maximum power output of 30 W using an irrigation rate of 10–20 mL/min (0.9% saline infused with the Cool Flow Pump, Biosense Webster). The ablation period was expanded for up to 2 min when a change of the PV conduction pattern was noted. However, energy application was stopped prematurely in case of catheter dislodgement. Furthermore, the catheter was moved slightly in order to expand the lesion in case of amplitude reduction >50% after an application time of 60 s. The selected endpoint of the PV isolation procedure was completely block indicated by elimination or dissociation of all PV potentials during sinus rhythm. This was validated by pacing at CS or LA appendage (LAA), if required. LAA pacing was systematically used in the setting of presumed atrial far-field potentials to exclude any persistent PV conduction. However, exit block apart from the emergence of dissociated PV rhythms was only investigated in case of any doubt of complete PV isolation, e.g. far-field potentials not originating from the LAA in the left PVs. Additional ostial ablation as previously described was performed in both groups when fractionated ostial potentials were detected. Special care was taken to keep the circumferential ablation line as proximal as needed to avoid PV stenosis or occlusion. Following CTI ablation a repeat investigation of all PVs was performed using the circumferential mapping catheter after a period of at least 30 min.

**Cavotricuspid isthmus ablation**

Right atrial isthmus ablation was performed in all patients using the previously described strategy. RF energy was applied using the point-by-point ablation technique with a maximum power of 50 W (irrigation rate 10–20 mL/min) until complete bidirectional block of the isthmus was confirmed by mapping of wide double potentials along the ablation line and by differential pacing.

**Left linear ablation**

In all patients randomized for additional left linear ablation (PVI + SM), three-dimensional reconstruction of the entire LA and the LA–PV junction was performed using the Ensite NavX™-system (Figure 1) as previously described. Following external

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**Figure 1** Posterior view of a three-dimensional LA reconstruction and MRI scan: a conventional electrode catheter is visible in the CS and a Lasso catheter placed in the right superior pulmonary vein (RSPV). A steerable mapping catheter used for creation of LA geometry is located proximal to the Lasso catheter. The peripheral aspects of the PVs are represented by light dots in order to focus the mapping and ablation approach to the ostial region and the LA body. At this time of the procedure all PVs were successfully isolated and effective ablation lines (roof and LA-isthmus) were deployed between both superior PVs (RSPV and LSPV) and between MA and LIPV. The induction of contiguous ablation lines was supported by non-fluoroscopic navigation and additional orientation on the MRI scan.
cardioversion and PVI, a contiguous ablation line was deployed during sinus rhythm connecting the posterior ablation line of the left and right superior PV at the posterior part of the superior LA. The LA isthmus line was deployed between posterior MA and LIPV. It was attempted to connect both anatomic structures using the shortest distance depicted by the three-dimensional reconstruction. RF was initially delivered at both lines for up to 50 W/60 s using a point-by-point dragging technique with an irrigation rate of 30 mL/min and a temperature limitation of 50 °C. Subsequently, the maximum power level was adjusted to 40 W after four patients following the reports of cases with cardiac tamponade during linear LA ablation.8 No epicardial ablation via the CS was performed in this cohort. The attempted endpoint of linear ablation in the LA was complete conduction block. This was validated for the LA isthmus line by differential pacing with bidirectional reversal of the peri-mitral activation sequence and the recording of local separated double potentials at the entire ablation line (Figure 2) as described by Jais et al.9 in comparison with the baseline situation. Incomplete effects were assumed when no complete reversal of the activation sequence but conduction delay was achieved. Mapping of the entire ablation line was performed in order to detect potential residual gaps. Evaluation of the roof-line was performed by mapping a corridor of double potentials along the line during LA appendage pacing. However, in the case of complete disappearance of all potentials at the LA roof, activation mapping of the posterior LA wall during LA appendage pacing was performed. A changed activation sequence from left-to-right to right-to-left in the presence of a blocked mitral isthmus line was considered as complete roof-line block.

Follow-up
All patients were hospitalized for at least 3 days. Anti-arrhythmic drug treatment (flecainide n = 3 PVI group, n = 3 PVI + SM group; propafenone n = 1 PVI group, n = 0 PVI + SM group; sotalol n = 1 PVI group, n = 2 PVI + SM group) was continued for up to 8 weeks in all cases, except patients with AF recurrences after more than 4 weeks post-ablation and those on amiodarone. In these patients

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/27/23/2871/2887127/12887127)

**Figure 2** Conduction block of the LA isthmus: prior to the ablation, conduction between LIPV and MA is present during CS pacing while the mapping catheter (Map dis and prx) is placed in the target region (A). The short interval between stimulus and local electrogram recorded via map at baseline (6, left panel) is markedly increased to 120 ms after ablation when map is located at the contralateral aspect of the ablation line (B, right panel). In addition, widely separated double potentials can be recorded along the ablation line. These findings are compatible with conduction block of the LA isthmus in counter-clockwise direction (C). Pacing via the distal tip of the mapping catheter (D) shows conduction block in clockwise direction because of an inferior to posterior activation of the CS (CS 5–6 earlier than CS 3–4). Further abbreviation: HRA, high right atrium.
can be impossible.

ence due to the fact that the differentiation using Tele-ECG criteria present study, suspected LA flutter was also considered as recur-

Transoesophageal echocardiography and MRI were repeated follow-

sistent AF prior to ablation was 7 (1–18) months. In all
case could be assessed with the enrolled patient cohort.

An interim analysis performed, as mentioned above, demonstrated a dramatic difference with regard to primary study hypothesis between both groups. Hence, the study was stopped prematurely. However, statistical significance could be assessed with the enrolled patient cohort.

**Results**

**Patients**

The study consists of 62 consecutive patients having AF history of 72 (range 18–120) months. Median duration of persistent AF prior to ablation was 7 (1–18) months. In all patients external cardioversion was mandatory to terminate AF episodes. Baseline characteristics of the patients are demonstrated in Table 1.

An interim analysis performed, as mentioned above, demonstrated a dramatic difference with regard to primary study hypothesis between both groups. Hence, the study was stopped prematurely. However, statistical significance could be assessed with the enrolled patient cohort.

**Procedural results**

PVI including a waiting period of 30 min was initially successful in 98% of all targeted PVs in both groups requiring a similar amount of RF duration (35.2 ± 13.1 vs. 32.5 ± 11.7 min, \( P = 0.49 \); Table 2). Additional RF application for LASM (23.7 ± 5.5 min) did not significantly increase the fluoroscopy time (72.1 ± 18.7 vs. 72.9 ± 17.3, \( P = 0.92 \)).

**Linear ablation**

Cumulative endocardial RFC delivery (15.6 ± 8.8 min) caused a bidirectional block demonstrated by differential pacing of the LA isthmus in 72% (23/32) of the cases. In the remaining nine patients, differential pacing revealed an incomplete block. The mean delay during pacing through the CS catheter septally from the isthmus line to the LA appendage was significantly longer in patients with a complete block as compared with those without (204 ± 24 ms vs. 151 ± 21 ms, \( P = 0.002 \)). In most cases with incomplete effects but delayed peri-mitral conduction, the site of shortest electrogram separation suggestive for a conduction gap was detected adjacent to the CS.

Complete conduction block for the roof-line was only demonstrable in 44% (14/32). In the remaining 56% (16 patients), neither a corridor of double potentials nor an activation sequence reversal on the posterior aspect of the roof-line was assessable. However, there was no significant difference of the mean delay during LA appendage pacing to the posterior aspect of the roof-line in comparison of patients with and those without assessable complete roof-line block (163 ± 34 vs. 139 ± 11 ms). Bidirectional block of the cavitricuspid isthmus could be achieved in all cases.

**Complications**

Two procedure-related complications occurred in patients assigned to PVI with additional SM. One patient experienced a cardiac tamponade during LA isthmus ablation with 50 W, which was immediately drained without further complications. After limiting the maximum power level to 40 W for LA isthmus ablation, neither a cardiac tamponade nor pericardial effusions occurred. Another patient had a minor ischaemic stroke accompanied by dizziness occurring the day after ablation. All patients recovered subsequently without sequelae.

**Follow-up**

**Early recurrences**

During the early post-interventional period (4 weeks), a substantial amount of patients following PVI \( n = 23 \) (77%) and PVI with additional SM \( n = 14 \) (44%) experienced AF recurrences documented by Tele-ECG \( P = 0.002 \). Early cardioversion (<4 weeks post-ablation) was required in eight patients after PVI and six patients after PVI + SM, respectively.

**Long-term follow-up**

All patients completed a follow-up time of more than 1 year (Figure 3). After a median overall follow-up time of 487 days (429–570), 6/30 (20%) patients undergoing PVI (median follow-up time: 471 days; range: 429–523) alone remained in SR as compared with 22/32 (69%; \( P = 0.0001 \)) following additional SM (median follow-up time: 513 days; range: 467–570). Recurrences more than 4 weeks after ablation were exclusively persistent in the PVI group, which were only paroxysmal in the PVI + SM group. In 9 out of those 10 patients with recurrences in the PVI + SM group, ablation of at least one line was incomplete including four patients with two incomplete lines (mitral isthmus: \( n = 5 \), roof-line:

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Main parameters of the ablation procedure</th>
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<tbody>
<tr>
<td></td>
<td>PVI + SM</td>
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<tr>
<td>PV-block</td>
<td>121/124 (98%)</td>
</tr>
<tr>
<td>RF-duration for PVI (min)</td>
<td>35.7 ± 13.8</td>
</tr>
<tr>
<td>RF-duration for SM (min)</td>
<td>23.7 ± 5.5</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>72.9 ± 17.3</td>
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*Figure 3* Follow-up of all patients with persistent AF: Kaplan–Meier curve depicting freedom of AF 4 weeks after exclusive pulmonary vein isolation (=PVI, dotted line) and PVI with additional SM (=PVI + SM, solid line; \( P = 0.0001 \)). This was defined as the lack of any symptomatic or asymptomatic AF episode (>30 s) documented by conventional or Tele-ECG recording.
n = 8). Only one patient with two incomplete lines was in sinus rhythm during follow-up. Among those patients with AF recurrences, LA flutter was presumed according to the Tele-ECG recording in one patient with PVI alone two patients with additional SM which also had an incomplete LA isthmus line. The episodes were persistent in two patients after PVI + SM. These patients subsequently underwent successful ablation of peri-mitral LA flutter following initial incomplete ablation of the LA isthmus resulting in complete block in both patients, requiring epicardial ablation via the CS in one.

Repeat MRI and transoesophageal echocardiography did not reveal narrowing or enhanced flow velocity in any of the investigated patients.

Discussion

The first main finding of the present study is the demonstration that PVI alone is insufficient for the treatment of patients with persistent AF. Second, adjunctive LA linear ablation is associated with a significantly higher success rate than PVI alone in those patients. Third, incomplete LA lines are associated with a high recurrence rate for AF and LA flutter. Finally, early post-procedural AF recurrences are not necessarily associated with a negative result during long-term follow-up after LASM with linear lesions.

Role of the PVs in AF maintenance

The PVs are the predominant trigger locations for AF initiation and subsequently have become the main target for interventional treatment of paroxysmal AF. There is emerging evidence that the PVs also play a critical role for AF maintenance in paroxysmal AF. Anatomical studies found a variable arrangement of muscle fibres at the atrio-venous junction and several animal studies demonstrated that these non-uniform arrangements of atrial muscle fibres extending into the PVs are associated with heterogeneous anisotropy, conduction delay, and block within the PVs and fractionated electrograms. Arora et al. demonstrated using high-resolution optical mapping that those conditions were capable of sustaining re-entry within the PVs.

Clinical studies have observed that the PVs and the veno-atrial region have distinctive electrophysiological properties. Jais et al. demonstrated significantly shorter ERP of the PVs in patients with paroxysmal AF (in some as short as 80 ms) compared with patients without a history of AF. Another study has shown that amiodarone treatment shortens the ERP of the PVs in patients with paroxysmal AF (in some as short as 80 ms) compared with patients without a history of AF and LA flutter. Finally, early post-procedural AF recurrences are not necessarily associated with a negative result during long-term follow-up after LASM with linear lesions.

According to the high success rates of surgical MAZE procedures, attempts have been made to reproduce these results by percutaneous catheter-based linear ablations. As the initial attempts to achieve complete lines of block within the left atrium using a conventional 4-mm tip ablation catheter were disillusioning, empirical linear ablation without verification of completeness were used to modify the LA substrate. Incomplete lines may not only create a substrate for re-entrant arrhythmias, but additionally it has been reported recently in a surgical study using cryoblation for left linear lesions that patients with incomplete lines are also prone to have a higher recurrence rate of AF. Three-dimensional navigation systems, such as Carto and Ensite NavX can be helpful, especially in guiding the deployment of contiguous linear lesions and thus reducing the risk for potentially proarhythogenic residual conduction gaps. In addition, reduction of fluoroscopy exposure during linear ablation has been shown.

As was supposed that the peri-mitral electrical activation plays a critical role for AF maintenance due to the fibre orientation and preferential propagation around the MA. Jais et al. implemented mitral isthmus ablation using an irrigated-tip catheter. This study demonstrated a high success rate in terms of completeness of the line (92%) and the procedural outcome (87% after 1 year). Hsu et al. reported in patients with AF and concomitant congestive heart failure that linear ablation at the LA roof and the mitral isthmus results in 69% of patients being free of AF and significantly increased LV function. Recently, Fassini et al. confirmed the additional benefit of mitral isthmus ablation in a randomized study. A subgroup analysis revealed the highest improvement of the success rate by the use of mitral isthmus ablation in patients with persistent AF. Nevertheless, the results of this subgroup analysis in patients with persistent AF have certain limitations: first, there are no data indicating the longest duration of an AF episode and the number of previous cardioversions demonstrating the severity of the arrhythmia. Second, anti-arrhythmic drug therapy with flecainide or amiodarone was continued for at least 6 months. Third, daily Tele-ECG submission was discontinued after 2 months of follow-up.

Nonetheless, LA linear ablation still remains technically challenging. In the study of Jais et al., 68% of patients required an ablation within the CS facing the endocardial aspect of the mitral isthmus because of persisting epicardial conduction. The mitral isthmus anatomy varies markedly, including its relation to the coronary circumflex artery (CX). Thus, it is rather surprising that there is only one...
reported case of an occlusion of the CX reported in a cohort of 500 patients who underwent mitral isthmus ablation with application within the CS.\textsuperscript{38} Furthermore, usually a high amount of RF applications are also required endocardially to achieve a complete block in the mitral isthmus.\textsuperscript{9} Finally, the main complication of mitral isthmus ablation is cardiac tamponade which is reported to have an incidence of 4\% in the study by Jais et al.\textsuperscript{9} In the present study, bidirectional block of the mitral isthmus line was demonstrable only in 72\% of patients. Due to concerns with regard to the complications mentioned earlier, no epicardial ablation via the CS was performed. Hence, in comparison with the results of Jais et al.,\textsuperscript{9} the incidence of complete block along the mitral isthmus only by epicardial RF applications. In comparison, Fassini et al.\textsuperscript{36} reported a complete mitral isthmus block in 76\% of patients including RF delivery from within the CS.

Although the exact mechanisms of AF prevention by linear lesions still remains not completely elucidated, several reasons may be relevant. Among those are the reduction of excitable LA myocardial mass, the attenuation of vagal innervation\textsuperscript{39} and the abolition of non-PV foci, especially those potentially related to the ligament of marshall.\textsuperscript{40} Also, the elimination of anchor circuits confined to the region of the LA–PV junction known for its distinctive anatomic and electrophysiologic properties may account for this effect.\textsuperscript{15,19,20} Furthermore, the additional deployment of linear lesions may have enhanced the likelihood of persistent PV block.

Limitations

The study included a relatively small number of patients limiting the evaluation of the expected importance of complete vs. incomplete block with regard to the primary endpoint. However, the major reason for the small study size is the significant difference of the success rates between patients with and those without an additional SM having a markedly worse procedural outcome. Hence, the study was stopped for ethical reasons before inclusion of the estimated patient number.

A complete conduction block only could be demonstrated for the mitral isthmus line in 72\% and for the roof-line in 44\%. In accordance to the results of Jais et al.,\textsuperscript{9} the preferential site for gap conduction was located at the endocardial aspect of the CS indicating persistent epicardial conduction. Thus, ablation within the CS may increase the rate of line completion but has not been performed in the present study. Electrogram evaluation because of spontaneous and ablation-induced scar may account for the limited number of definite roof-line block. However, as the mean delay to the posterior aspect of the roof-line during LA appendage pacing was not significantly different in patients with and those without demonstration of complete block, some cases with roof-line block perhaps were missed because of the absence of detectable atrial potentials.

Tele-ECG recordings may miss asymptomatic recurrences because of a declining compliance with regard to daily transmission. Although, asymptomatic episodes after AF ablation have been recently reported to occur frequently (54\%), exclusively asymptomatic patients (9\%) are rare.\textsuperscript{41} Therefore, it seems very unlikely, that patients with recurrent AF may have been undetected in the present study. However, future studies with extended follow-up are required to assess the long-term effects of PVI + SM.

Conclusions

PVI alone is insufficient in the treatment of persistent AF, however, PV isolation in combination with SM by complete LA linear lesion can achieve a success rate similar to those of patients with paroxysmal AF. As demonstrated in previous studies using other strategies aiming for SM, early AF relapse is not necessarily associated with a negative outcome.

Conflict of Interest: The authors (S. Willems, H. Klemm, T. Rostock, D. Steven and B. Lutomsky) received speakers fee from St. Jude Medical.

References


