Left Atrial Appendage Electrical Isolation and Concomitant Device Occlusion to Treat Persistent Atrial Fibrillation

A First-in-Human Safety, Feasibility, and Efficacy Study

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Background—Left atrial appendage (LAA) electric isolation is reported to improve persistent atrial fibrillation (AF) ablation outcomes. However, loss of LAA mechanical function may increase thromboembolic risk. Concomitant LAA electric isolation and occlusion as part of conventional AF ablation has never been tested in humans. We therefore evaluated the feasibility, safety, and efficacy of LAA electric isolation and occlusion in patients undergoing long-standing persistent AF ablation.

Methods and Results—Patients with long-standing persistent AF (age, 68±7 years; left atrium diameter, 46±5 mm; and AF duration, 25±15 months) underwent AF ablation, LAA electric isolation, and occlusion. Outcomes were compared with a balanced (1:2 ratio) control group who had AF ablation alone. Among 22 patients who underwent ablation, LAA electric isolation was possible in 20. Intraprocedural LAA reconnection occurred in 17 of 20 (85%) patients, predominantly at anterior and superior locations. All were reisolated. LAA occlusion was successful in all 20 patients. There were no major peri-procedural complications. Imaging at 45 days and 9 months confirmed satisfactory device position and excluded pericardial effusion. One of twenty (5%) patients had a gap of ≥5 mm requiring anticoagulation. Nineteen of twenty (95%) patients stopped warfarin at 3 months. Without antiarrhythmic drugs, freedom from AF at 12 months after a single procedure was significantly higher in the study group (19/20, 95%) than in the control group (25/40, 63%), P=0.036. Freedom from atrial arrhythmias was demonstrated in 12 of 20 (60%) and 18 of 20 (90%) patients after 1 and ≤2 procedures (mean, 1.3), respectively.

Conclusions—Persistent AF ablation, LAA electric isolation, and mechanical occlusion can be performed concomitantly. This technique may improve the success of persistent AF ablation while obviating the need for chronic anticoagulation.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT02028130.

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Key Words: atrial appendage ■ atrial fibrillation ■ catheter ablation ■ thromboembolism ■ warfarin

Catheter ablation has transformed the treatment of atrial fibrillation (AF)2; however, the rhythm outcomes in treating persistent AF are variable, often requiring multiple procedures to maintain long-term freedom from atrial arrhythmias.3–5 Electric isolation of the pulmonary veins (PVs) is central to catheter ablation strategies4; however, focal sources and other arrhythmic substrates outside the PVs have been found to play a key role in maintaining persistent AF.6–7 The left atrial appendage (LAA) has been shown to be a particularly important source of foci perpetuating AF8–9. Consequently, LAA electric isolation may improve freedom from AF.5,7,10,11 However, ablation within the LAA carries a risk of perforation,12 whereas ostial electric isolation of the LAA without occlusion carries a risk of thromboembolism.13 The combination of conventional AF ablation with LAA electric isolation and occlusion within a single procedure may be synergistic in improving the success rate of ablation while also mitigating stroke risk and reducing the bleeding risk of long-term anticoagulation.

See Editorial by Di Biase and Natale

We have recently demonstrated in canines that this procedure is both feasible and safe.14 However, the feasibility, safety, and efficacy of this procedure in humans are not known.

Methods

The study protocol is summarized in Figure 1. Extended methodology details are given in the Data Supplement.

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What is known

- The left atrial appendage (LAA) can be an important focus for persistent AF initiation, propagation, and recurrence following ablation.
- More than 90% of thrombi occurring in patients with nonvalvular atrial fibrillation occur in the LAA. Percutaneous LAA occlusion has been demonstrated to have a similar stroke risk to warfarin in patients with AF.

What the study adds

- The addition of LAA electrical isolation to a conventional AF ablation protocol, combined with LAA occlusion, is shown to be feasible.
- This concomitant technique has the potential to improve ablation outcomes, mitigate stroke risk, and reduce bleeding risk by reducing long-term anticoagulation.

Patients

Enrollment criteria were age ≥18 years, long-standing persistent AF (>12 months), and CHA2DS2-VASc score of ≥1. Patients with persistent AF awaiting ablation were consecutively screened and prospectively enrolled in this case-control pilot study across 2 UK sites between July 2013 and April 2014. Exclusion criteria included previous AF ablation and LAA ostial diameter of >33 mm; complete exclusion criteria are listed in the Data Supplement.

All procedures were performed after obtaining written informed consent. The study protocol was approved by the regional ethics committee. Baseline assessments are summarized in Figure 1.

Oral Anticoagulation

Patients were established on long-term anticoagulation with warfarin with a target International Normalized Ratio of 2.5 to 3.0 for at least 4 weeks before the procedure; this regime was uninterrupted for the procedure.

Catheter Ablation of AF

Catheter ablation was guided by a 20-pole circular PV catheter (Lasso, Biosense Webster, Diamond Bar, CA), 3-dimensional mapping (Carto 3, Biosense Webster), and conventional electrophysiology recording (LabSystem Pro, Bard, Lowell, MA) systems. Ablation was performed with an open-irrigated, 3.5-mm tip ablation catheter (SmartTouch Thermocool, Biosense Webster), limiting power to 30 W in most areas.

The PVs were electrically isolated with wide area circumferential ablation, and linear ablation was performed at the left atrial roof, lateral mitral valve isthmus, and cavotricuspid isthmus.

LAA Ablation and LAA Closure

Aiming for a contact force of 15g to 20g, higher power (35 W) was used to ablate at the atrial side of the LAA ostium, in view of potentially greater tissue thickness in this area. Additional ablation was performed at the left superior pulmonary vein (LSPV)-LAA ridge on both the pulmonary venous and LAA sides (Figure 2A and 2B). After isolation of the LAA (Figure 2C), a 60-minute observation

![Figure 1](http://circres.ahajournals.org/doi/abs/10.1161/CIRCRESAHA.117.041193)
Figure 2. Left atrial appendage (LAA) electric isolation. **A**, Ablation of the LAA. Anteroposterior fluoroscopic view of the ablation catheter (at the LAA ostium), 20-pole circular catheter (distal to the LAA ostium), and 10-pole catheter (within the coronary sinus) arrangement during LAA ablation. **B**, Left lateral 3-dimensional anatomic image demonstrating ablation lesions at the anterior, superior, and inferior LAA ostial margins (light blue) and at the posterior LAA ostium (red) adjacent to the LAA–left superior pulmonary vein (LSPV) ridge. **C**, Intracardiac electrograms from the same patient demonstrating the slowing of LAA potentials followed by isolation of LAA during ablation. Occlusion device implantation in right anterior oblique fluoroscopic view. **D**, Contrast injection into LAA post isolation. The site of the LAA ostium is illustrated with a dashed line. **E**, After release of the occlusion device.
period ensued to identify early LAA reconnection. At the beginning of this period, bidirectional conduction block of all previous lesions was confirmed and additional ablation was performed if required. Entrance and exit block of the LAA were reassessed before and after administration of 12-mg intravenous adenosine bolus.16 When reconnection was identified, the LAA was reisolated. For standardization between the study and control groups, acute PV reconnection was not assessed using adenosine. The LAA was then occluded with an appropriately sized Watchman device (Boston Scientific, Marlborough, MA), as has previously been described in detail,17 using the existing transseptal puncture (Figure 2D and 2E). Key implantation measurements included device compression ratio (final device diameter/original device diameter, %) and device protrusion from LAA ostium (mm).

Ablation End Points

1. Entrance block: the absence or dissociation of PV and LAA potentials when compared with local left atrial (LA) potentials, recorded by the Lasso catheter positioned sequentially in the PVs and LAA.
2. Exit block: the dissociation of PV and LAA potentials when compared with local LA potentials, confirmed during pacing from the Lasso catheter positioned sequentially in the PVs and LAA, showing local capture and dissociation with the atrial activity.
3. Linear ablation block: bidirectional conduction block across the line confirmed by means of differential pacing.14

LA Pressure and LAA Physiological Assessments

Intraprocedural measurements of LAA depth and ostial size, LAA outflow and inflow velocities by transesophageal echocardiography (TEE), and left atrial pressure via the left atrial sheath were recorded at 3 separate time points (post-transseptal puncture, post-AF ablation, and post-LAA isolation) to characterize the influence of each part of the ablation procedure on these parameters. Left atrial pressure was additionally measured after LAA closure.

Follow-Up

Patients were followed up at 45 days, 3 months, 6 months, 9 months, and 12 months (Figure 1).

Rhythm Monitoring and Further Procedures

Seven-day continuous ECG monitoring (R-test Evolution 4, Novacor, Paris, France) was performed at 3, 6, 9, and 12 months. Two experienced cardiac physiologists independent and blinded of the study interpreted the results. Where there was ambiguity, there was a consensus opinion of an independent blinded electrophysiologist. If persistent atrial arrhythmia recurred during a prespecified 3-month blanking period, the patient was treated by electric cardioversion. When atrial arrhythmia recurred outside of the blanking period, a second catheter ablation procedure was offered. Class I and III antiarrhythmic drugs were stopped within the blanking period. If repeat ablation was performed, direct assessment of LAA conduction was not possible; however, we mapped for far-field LAA electric activity within the LSPV. Warfarin was also continued until at least 2 months after repeat ablation.

Imaging

Computed tomographic scan and TEE were performed at 45 days to assess the device location, identify gaps or thrombus, and detect any effect impingement on the LSPV or mitral valve. If appearances were satisfactory with no gaps of ≥5 mm, warfarin was stopped 6 weeks later and replaced with 75-mg aspirin once daily. Transesophageal echocardiogram was performed at 6 months to compare left atrial dimensions with baseline. TEE was repeated at 9 months to detect any perdevice gaps or thrombus formation.

Study End Points

The primary efficacy end point was a successful LAA electric isolation and occlusion. The safety end point was the absence of any major procedure-related complication or thromboembolic event during follow-up. The secondary end points were single-procedure atrial arrhythmia–free survival, AF-free survival, and atrial arrhythmia–free survival time (all defined by symptoms and ECG monitoring, off antiarrhythmic drugs, with the duration of ≥30 s, to 12 months, and outside of blanking period), LA size (by transthoracic echocardiogram at 6 months), and AFEQT (Atrial Fibrillation Effect on Quality of Life questionnaire) quality of life score (at 12 months).

Histological Assessment of the LAA Ostium

Ten human hearts matched for the duration of continuous AF and left atrial size, which had not undergone ablation or LAA occlusion, were studied for comparison. Histological assessment of the regional variation in LAA ostial thickness was performed to correlate with potential areas of acute reconnection (Figure 3B through 3E). Hearts were incised laterally through the left atrium and ventricle to expose the LAA ostium. Digital images were obtained using the Canon Rebel XSi system. Sections were taken in 4 quadrants (superior, inferior, anterior, and posterior) relative to the LAA ostium. Digital images of the sections were obtained before processing. The tissue sections were dehydrated in a graded series of ethanol, infiltrated, and embedded in paraffin. Each block was sectioned at 4 to 6 µm, mounted onto slides, and stained with hematoxylin and eosin and Movat pentachrome. Subsequently, Movat-stained slides were scanned using the ZEISS Axio Scan.Z1 (Carl Zeiss Microimaging, Inc, Jena, Germany). Morphometric analysis was performed using Zen 2012 Blue Edition (Carl Zeiss Microimaging, Inc), and measurements were taken of the area representing the LAA–LA junction.

Control Group

We compared the rhythm outcomes (12-month single-procedure atrial arrhythmia–free survival, AF-free survival, and atrial arrhythmia–free survival time) of the study patient group with those of a balanced control group. A database of 171 consecutive persistent AF patients undergoing AF catheter ablation during the same time interval as the study group was examined. Study patients were balanced with controls by age, sex, presence of structural heart disease, duration of continuous AF, LA dimensions, and AF ablation lesion set (excluding LAA isolation). This was performed blinded to procedural outcome. From this subgroup of balanced patients, 40 (1:2 ratio of study to controls) consecutive patients were selected to become the control group. Follow-up in the control group was similar to the study group (Holter ECGs at 3, 6, and 12 months), and rhythm outcomes were assessed independently and blinded.

Statistical Analysis

Continuous data are presented as mean±SD, mean (95% confidence interval), median (interquartile range), and comparisons made using the Student t test. Categorical data are presented as frequency/percentage and comparisons made using the Fisher exact test in view of the relatively small sample size. The Kaplan–Meier method was used for graphical assessment of time-related events. All patients without an event or lost to follow-up were censored at the time of the last known event status. Cox proportional hazards regression was used to assess for differences in atrial arrhythmia recurrence and quality of life scores between the study and control groups. A 2-sided P<0.05 was considered statistically significant. All data were analyzed using Stata 12 (Statacorp, College Station, TX).

Results

Patients

Forty-eight patients were prospectively screened for inclusion; 23 were enrolled and underwent baseline investigations.
One patient was excluded because their baseline computed tomographic scan demonstrated an LAA ostial diameter of >33 mm. Twenty-two patients were included into the study (Figure 4). Baseline characteristics of the study patients and controls are summarized in Table 1.

**Index Procedure**

Bidirectional block of all PVs, roof, lateral mitral valve isthmus, and cavo-tricuspid isthmus was achieved in all 22 patients. Additional coronary sinus (CS) ablation was required to achieve bidirectional block across the mitral isthmus in 12 of 22 (55%) cases, during which the CS was isolated in its distal portion in 2 of 22 (10%) cases. Before LAA ablation, far-field LAA signals were seen within the LSPV in all cases. The LAA was electrically isolated in 20 of 22 (91%) cases (mean ablation time, 25.4±19.2 minutes). Additional distal CS ablation was required to achieve LAA isolation in 8 of 20 (40%) cases. Far-field LAA signals were no longer visible within the LSPV after isolation. In 2 cases, there were anatomic anomalies that prevented successful LAA isolation. In the first case, an acute, retrograde angulation of the mid to distal LAA resulted in the distal LAA being in direct contact with the anterolateral left atrial epicardial wall. There was therefore a residual sleeve of electric conduction between the distal LAA and LA that we were unable to safely ablate to isolate the LAA. In the second case, there was a residual, patent vascular connection between the distal CS and anterior LAA that was discovered during epicardial ablation of the LAA via...
the CS. This resulted in a persistent sleeve of conduction tissue that we were unable to completely ablate.

The procedural parameters are summarized in Table 2. The 2 patients in whom LAA isolation was not achieved did not receive an LAA closure device and were excluded from further analysis of the main cohort. The remaining 20 patients became the study population. Acute reconnection of the LAA occurred in 17 of 20 cases during the 60-minute waiting time.

Table 1. Characteristics of Study Patients (n=20) and Their Balanced Controls (n=40)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Population (n=20)</th>
<th>Control Population (n=40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>68±7</td>
<td>67±6</td>
<td>0.57</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (35%)</td>
<td>14 (35%)</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>13 (65%)</td>
<td>26 (65%)</td>
<td>1</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>3 (15%)</td>
<td>6 (15%)</td>
<td>1</td>
</tr>
<tr>
<td>Duration of continuous AF, mean±SD, mo</td>
<td>25±15</td>
<td>24±12</td>
<td>0.78</td>
</tr>
<tr>
<td>LA size, mean±SD, mm</td>
<td>46±3</td>
<td>45±4</td>
<td>0.33</td>
</tr>
<tr>
<td>Lesion set, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV isolation</td>
<td>20 (100%)</td>
<td>39 (98%)</td>
<td>1</td>
</tr>
<tr>
<td>Roof line</td>
<td>20 (100%)</td>
<td>39 (98%)</td>
<td>1</td>
</tr>
<tr>
<td>Lateral MVI line</td>
<td>20 (100%)</td>
<td>35 (88%)</td>
<td>0.16</td>
</tr>
<tr>
<td>CTI line</td>
<td>20 (100%)</td>
<td>40 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>CHA2DS2-VASc, mean±SD</td>
<td>3.1±1.2</td>
<td>3.0±1.6</td>
<td>0.81</td>
</tr>
<tr>
<td>HAS-BLED, mean±SD</td>
<td>2.5±1.1</td>
<td>2.3±1.3</td>
<td>0.56</td>
</tr>
<tr>
<td>Radiofrequency ablation duration, mean±SD, min</td>
<td>89.6±23.4</td>
<td>73.4±19.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Total procedure time, min*</td>
<td>276.0±46.6</td>
<td>211.2±49.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HAS-BLED scoring system to assess 1-year risk of major bleeding in patients with atrial fibrillation. AF indicates atrial fibrillation; CTI, cavotricuspid isthmus; LA, left atrium; MVI, mitral valve isthmus; and PV, pulmonary vein.

*Including mandatory 60-minute wait time after LAA electric isolation. This was not included in the control cases.
revealed by adenosine bolus in the 20 patients. After the 60-minute wait, no further LAA reconnections were reisolated with further ostial LAA ablation (8.1±6.5 minutes).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total procedure time</td>
<td>276.0±46.6 min*</td>
</tr>
<tr>
<td>Total ablation time</td>
<td>89.6±23.4 min</td>
</tr>
<tr>
<td>Total LAA ablation time</td>
<td>33.5±27.7 min</td>
</tr>
<tr>
<td>Fluoroscopy time</td>
<td>39.3±13.3 min</td>
</tr>
<tr>
<td>Fluoroscopy dose</td>
<td>10212±5595 mGy</td>
</tr>
<tr>
<td>Pulmonary veins successfully isolated</td>
<td>88/88 (100%)</td>
</tr>
<tr>
<td>Roof, MVI, and CTI lines successfully blocked</td>
<td>22/22 (100%)</td>
</tr>
<tr>
<td>LAA successfully isolated</td>
<td>20/22 (91%)</td>
</tr>
<tr>
<td>Acute LAA reconnections (all reisolated by radiofrequency ablation)</td>
<td>17/20 (85%)</td>
</tr>
<tr>
<td>During 60-min wait</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>Post-adenosine bolus</td>
<td>0/20</td>
</tr>
<tr>
<td>Additional CS ablation to achieve LAA isolation</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td>LAA successfully isolated at the end of procedure</td>
<td>20/22 (91%)</td>
</tr>
<tr>
<td>Device successfully implanted</td>
<td>20/20 (100%)</td>
</tr>
<tr>
<td>No. of devices used per case</td>
<td>1.05±0.22</td>
</tr>
<tr>
<td>Device size</td>
<td>27.3±3.1 mm</td>
</tr>
<tr>
<td>Device implant time</td>
<td>22.6±8.6 min</td>
</tr>
<tr>
<td>Device compression (% change in diameter)</td>
<td>81±7%</td>
</tr>
<tr>
<td>Device protrusion</td>
<td>7.5±2.3 mm</td>
</tr>
<tr>
<td>Total fluid input</td>
<td>3172+928 mL</td>
</tr>
</tbody>
</table>

LA Pressure and LAA Physiological Assessments

There was a significant increase in LAA ostial diameter between the baseline and post-LAA ablation measurements (19±2 mm versus 21±2 mm; P=0.02). This corresponded with a significant increase in LA pressure between the baseline (immediately post-transseptal puncture) and post-LAA isolation studies (12±4 versus 17±3 mm Hg; P=0.01) and the post-linear ablation and post-LAA isolation studies (15±4 versus 17±3 mm Hg; P=0.006), Table 3. There was no significant change in LA pressure between the post-LAA isolation and post-LAA closure studies.

LAA Occlusion

LAA occlusion was successfully completed in all 20 cases in which it was attempted after successful LAA isolation. There were no residual gaps. Device compression (81±7%) and protrusion (7.5±2.3 mm) were satisfactory. The primary efficacy end point was met in 20 of 22 (91%) cases. There were no periprocedural complications.

Follow-Up

Forty-Five–Day Computed Tomography and TEE

There were no changes in position or in compression measurements of any device. One of twenty (5%) cases had a gap of ≥5 mm, requiring continued anticoagulation. Nineteen of twenty (95%) met criteria to stop warfarin at 3 months. There was no evidence of PV stenosis or extrinsic compression from the device of the LSPV in particular. The circumflex artery lumen was uncompromised.

Six-Month Transthoracic Echocardiogram

The indexed left atrial volume significantly decreased at 6 months compared with baseline (mean difference, −5.12 cm³ [−8.12 to −3.87 cm³]; P=0.002).

Nine-Month TEE

Nineteen of twenty (95%) patients had unchanged appearances compared with their 45-day TEE. The remaining patient, 1 of 20 (5%), developed a 1×2-mm thrombus adherent to the device surface (without peridevice gaps), requiring anticoagulation resumption. This patient had undergone repeat ablation for atrial tachycardia at 3 months and had stopped warfarin at 5 months.

Arrhythmia Recurrence

Electric cardioversion was required during the blanking period in 2 patients, one of whom remained arrhythmia free for the remainder of the study. Eight patients had atrial arrhythmia recurrence outside the blanking period (1 AF and 7 atrial tachycardia [AT]). Six patients had a further ablation procedure during follow-up: 4 for persistent AT, 1 for paroxysmal AT, and 1 for persistent AF. The AT mechanisms were (1) perimital flutter followed by roof-dependent AT, (2) low posterior LA wall focal AT, (3) roof-dependent AT, and (4) perimital flutter. Termination of AT to sinus rhythm was achieved in all 4 cases of persistent AT.

PV reconnection was seen in 4 of 6 of the redo procedures. In 2 of these 4, PV reconnection was unrelated to the persistent AT. The remaining 2 cases had recurrence of persistent AF (PV reisolation terminated AF to a mitral
isthmus–dependent AT) and paroxysmal AT (clinical AT was noninducible after PV reisolation), respectively, related to PV reconnection.

There was no evidence of far-field LAA electric activity within the LSPV—in particular, within the anterior (LAA) border of the LSPV—in any of the 6 cases, thereby indicating no late LAA reconnection.

Of the remaining 2 patients with AT, 1 developed persistent AT at 97 days and declined ablation—they cardioverted to sinus rhythm with oral flecainide and remained asymptomatic in sinus rhythm for the remainder of the study. The final patient developed a short (6.2-minute) episode of asymptomatic AT at 12 months.

Complications
There were no major periprocedural complications and no thromboembolic events periprocedurally or during follow-up. Therefore, the primary safety end point was met in all cases.

There was one chest infection post procedure, which resolved after 48 hours. Another patient had an urticarial reaction that resolved after 72 hours. This may have been related to anesthesia as a similar reaction had previously occurred during a noncardiac procedure. One patient with a pre-existing history of quiescent esophageal varices had an upper gastrointestinal bleed at 7 months having stopped warfarin and started aspirin at 3 months. The varices were subsequently banded, and aspirin was stopped with no further recurrence of bleeding.

Histological Analysis
Examination of 10 matched human hearts (continuous AF duration of 30±16 months versus 25±15 months [study patients], P=0.40; and left atrial size of 48±5 mm versus 46±3 mm [study patients], P=0.18) demonstrated that the thickest LAA ostial areas were at the anterior (2.5±0.8 mm [range, 1.4–4.0 mm]) and superior (2.4±1.2 mm [range, 1.1–4.8 mm]) margins. The inferior (1.6±0.8 mm [range, 0.6–3.6 mm]) and posterior (1.6±0.8 mm [range, 0.8–2.9 mm]) margins were significantly less thick (P<0.02; Figure 3). These findings correlated well with the recorded sites of acute reconnection.

Discussion
This is the first clinical study to evaluate a strategy of concomitant LAA electric isolation and occlusion with a Watchman device as part of a standard persistent AF ablation. We found that the approach was not only feasible but also safe and at least as effective in maintaining sinus rhythm as conventional AF ablation.

From an embryological perspective, the LAA is the remnant of the primitive LA, formed by the adsorption of the nascent PVs and their branches during the fourth week of embryonic development.18 The junction between the LA and LAA contains anisotropic tissue with a complex fiber orientation, which results in electrophysiological properties that may predispose this region to support anatomic reentry or anchor functional rotors.19 It is thus plausible that the LAA may initiate AF akin to the PVs and could explain a role of the LAA in maintaining persistent AF.19

Prolongation of AF cycle length during ablation of persistent AF heralds AF termination. Researchers have previously demonstrated that the increase in AF cycle length (measured in the CS, right atrial appendage, and LAA) during ablation of the LAA is significantly greater than the prolongation observed during ablation at other sites (8.9±6.2 ms versus 3.8±6.4 ms; P=0.0001).8 Notably, when ablation sites were randomized in sequence, the LAA emerged as an important region where significant cycle length prolongation (≥25 ms) or AF termination was demonstrated in 59% of patients.6

A large registry study (n=987) demonstrated that 27% of recurrences in patients who had undergone AF ablation (18% paroxysmal and 82% nonparoxysmal) involved an LAA focus; critically, in 8.7%, the LAA was the only source of AF.7 Furthermore, if the LAA was not ablated and electrically isolated, the postprocedure AF or atrial tachycardia recurrence rate was 74%, compared with 15% when the LAA was successfully isolated (P<0.001). Similarly, another cohort study has demonstrated that LAA electric isolation improves the clinical outcome in repeat ablation of long-standing persistent AF.8 An ongoing randomized controlled trial (BELIEF trial [Effect of Empirical Left Atrial Appendage Isolation on Long-Term Procedure Outcome in Patients With Persistent of Long-Standing Persistent Atrial Fibrillation Undergoing Catheter Ablation]),20 which seeks to determine whether empirical LAA isolation along with a standard ablation protocol is superior to the standard approach alone, may corroborate these findings. However, the standard anticoagulation
regimen with warfarin, that this trial uses, may not provide sufficient protection against the thromboembolic risk of an electrically isolated LAA.\textsuperscript{13}

Two major safety concerns arise when considering the techniques of LAA ablation. First, the thin aspects of the LAA wall may be prone to perforation.\textsuperscript{12,21} However, no conclusive data exist on the optimal ablation strategy to minimize this risk. Second, the electrically isolated, noncontractile LAA is a highly thrombogenic source.\textsuperscript{13}

**LAA Occlusion**

Many percutaneous LAA occlusion devices have been developed,\textsuperscript{17} although, at present, randomized controlled data are only available for the Watchman device. The randomized

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**Figure 5.** Twelve-month atrial arrhythmia (A) and atrial fibrillation (AF)-free (B) estimation after a single ablation procedure, off antiarrhythmic drugs, in study and case-control groups. The blanking period was set at 3 mo, after which occurrence of documented atrial tachyarrhythmia $>30$ s constituted procedural failure. AT indicates atrial tachycardia.
PROTECT AF study (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation), comparing the efficacy of this device to treatment with warfarin, showed that the device was noninferior in terms of stroke, systemic embolism, or cardiovascular or unexplained death in patients with nonvalvular AF. Subsequently, 4-year follow-up data showed statistically superior rates of cardiovascular death, all-cause mortality, and hemorrhagic stroke in the Watchman group. A more recent randomized study of Watchman versus warfarin (PREVAIL [Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy]) has been reported, although the event rates in both arms were similar, with an unexpectedly low event rate in the warfarin arm.

Procedural Feasibility
Having previously demonstrated this in canines, in this study we have shown for the first time in humans that in addition to a standard AF ablation protocol, concomitant LAA electric isolation and occlusion is feasible. We were able to achieve LAA electric isolation in all but 2 cases (20/22) and successfully implanted occlusion devices in all of these.

The LAA ostial diameter might be expected to decrease in size with circumferential ostial ablation, because of ablation-related edema; however, we found that it actually significantly increases in size (Table 3), as seen in our canine model. This correlates with a significant increase in LA pressure, presumably because of fluid infused during ablation. It is therefore important to make LAA sizing measurements after completing ablation to correctly size an LAA closure device.

Interestingly, after cessation of ablation, there was no further increase in LA pressure after LAA closure, despite excluding a capacitance chamber such as the LAA. This phenomenon may be a result of the LA demonstrating minimal resistance to expansion at relatively low pressures, thereby leading to minimal increases in LA pressure.

Ablation within the distal CS was frequently required to isolate the LAA; however, there is limited literature on this technique. CS ablation may interrupt the distal leftward extension of the Bachmann bundle at the epicardial aspect of the mitral isthmus and, therefore, isolate part of the LAA. In addition, the adjuvant use of distal CS ablation when required may have contributed to our ability to achieve acute mitral valve isthmus block in all study cases. However, because of the small sample size, this was not significantly greater than that achieved in the control group (100% versus 88%; P=0.10). Acute LAA reconnections occurred in 85% of cases (17/20) and were usually at the anterior and superior margins, in keeping with the increased thickness seen at those sites in our cadaveric hearts (Figure 3). Interestingly, there was no evidence of acute LAA reconnection after adenosine bolus in any case, although we have previously shown adenosine-induced acute LAA reconnection in a canine model. This finding was perhaps because of extensive ablation at higher power (35 W versus 30 W) at the LAA ostium.

The limited data on late LAA reconnection after circumferential electric isolation show rates of 12.5% (1/8 cases) at 45 days in a canine model and 15% (25/167 cases) at 12 months in a large registry study. In the 6 patients who underwent repeat ablation in our study, there was no evidence of LAA reconnection as determined by the absence of far-field LAA electric activity within the anterior (LAA) border of the LSPV. It is possible that such activity was abolished by local ablation or the presence of the device margins, rather than by LAA isolation. Although far-field LAA electrograms are an indirect measurement and, therefore, only a potential indicator of LAA reconnection, they were present within the anterior LSPV border at the index procedure in all cases pre-LAA isolation and were no longer visible within the LSPV after isolation in all cases. Therefore, even taking the aforementioned factors into account, LAA reconnection is unlikely in the absence of far-field LAA electrograms within the LSPV.

A possible alternative approach would be to perform the LAA closure procedure some weeks after the index ablation. This would permit LAA reisolation in the event of reconnections but would need to be balanced by the short-term risk of thromboembolism and the need for a second procedure.

Alternative Devices
Of the other LAA occlusion devices that are currently available, epicardial LAA occlusion with the LARIAT device may have a theoretical advantage of achieving occlusion and isolation in the same setting. However, at present, published data on the initial experience of combining this technique with percutaneous AF ablation has been with a sequential procedure in 2 sittings because of bleeding complications encountered when performing this as a concomitant procedure. There are also concerns about potentially high complication rates with the LARIAT suture delivery device technique. The use of other LAA occlusion devices for this purpose is also theoretically possible but untested.

Procedural Safety
Theoretical safety concerns center around the possibility of LAA ostial edema leading to over- or undersizing of the device, the resultant necrosis of the atrial wall or device migration, and PV stenosis. None of these complications were observed despite detailed imaging >9 months, nor were there any major periprocedural complications. In addition, there was no evidence of LAA ostial size reduction after extensive ablation around the ostia.

In humans, late peridevice gaps have been shown to occur in previously well-sealed LAA. This phenomenon was not seen in this study between 45 days and 9 months, although 1 patient had developed a gap by 45 days that persisted at 9 months. An asymptomatic sessile thrombus was detected on the device surface of another patient at 9 months, which was not present at 45 days or at 3 months (redoablation), and resolved on repeat TEE after 6 weeks of anticoagulation. Because ablation was performed 117 days after LAA closure, the device may only have been covered by a thin layer of endothelial tissue, which could be potentially injured during catheter movement and thus promote thrombus formation. On the basis of this possibility, in similar circumstances after redoablation, we would recommend follow-up TEE examination before termination of oral anticoagulation.
Procedural Efficacy
Left atrial size was reduced by ablation, consistent with previous observations of positive left atrial remodeling in patients with persistent AF; and the AFEQT score improved significantly.

The 12-month single-procedure freedom from atrial arrhythmia was higher in the study group (60% versus 40%) than in the control group, but it did not achieve statistical significance. Recurrences were dominated by AF rather than AF, a well-recognized phenomenon in the setting of extensive linear ablation. Notably, the single-procedure AF-free survival (95%) was significantly greater than in the control population (63%; P=0.036). This novel finding may lend weight to the hypothesis that the LAA plays a key role as a driver in persistent AF.

The 12-month atrial arrhythmia–free survival rate after 1 or 2 procedures was 95% (19/20) with a mean of 1.3 (range, 1–2) procedures per patient. This is significantly higher than the expected 12-month multiprocedure atrial arrhythmia–free success rate for comparable patients from a large registry of 63.1%, P=0.0007. The study procedure therefore seems at least as effective as a conventional AF ablation in terms of rhythm outcome. Despite this study having a small sample size that was not powered to detect small differences in outcome, there is a signal that the procedure has a trend toward a higher arrhythmia-free survival, and specifically, significantly greater freedom from AF (Figure 4A and 4B).

Limitations
In this pilot study, the relatively small number of patients and nonrandomized study design were limitations. However, it clearly demonstrates feasibility and, as we have previously demonstrated in canines, confirms that ostial LAA ablation does not prohibit occlusion device implantation in the same procedure. This experience will ultimately require further evaluation in a randomized controlled trial.

There are inherent limitations in using a retrospective control group. However, we balanced both groups across multiple relevant parameters to improve comparability and performed this blinded to procedural outcome to minimize bias. The control group therefore provides a representation of our usual institutional success rates for conventional AF ablation in similar patients against which the study group outcomes can be compared. The additional time required for LAA ablation in the study protocol provided an extended period after which PV and linear ablation reconnections could be identified and ablated. This may be an additional factor that improved outcome compared with the control group. This study complied with the ECG monitoring for persistent AF ablation recommended by the international consensus statement of 2012; however, silent episodes of paroxysmal AF might have been missed during follow-up. However, in this population with previous persistent AF, the presence of sinus rhythm on multiple visits confirms at least a major reduction in arrhythmia burden.

Conclusions
While LAA electric isolation may improve the clinical success in ablating persistent AF, the thromboembolic risk of the residual electrically inert appendage is a concern. Concomitant LAA occlusion after electric isolation may be a natural progression in treating persistent AF. This study demonstrates for the first time in humans the feasibility, safety, and efficacy of this combined approach.

Future randomized controlled trials may now further assess this technique that, in a single procedure, has the potential to improve ablation success rates and obviate the need for chronic anticoagulation.

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Supplemental Methods

Patients

_Exclusion criteria:_

Catheter or surgical AF ablation, LAA ostial diameter >33mm, pregnancy, prior atrioventricular nodal ablation or complete heart block with a permanent pacemaker, contraindication to anticoagulation, persistent thrombus in left atrium despite anticoagulation, active malignancy, life expectancy < 6 months, cerebrovascular accident within previous 6 months, reversible causes of AF including thyroid disorders, acute alcohol intoxication, recent major surgical procedures/trauma, cardiac events (myocardial infarction, percutaneous coronary intervention, valve or coronary bypass surgery) within previous 3 months, previous heart transplant, severe neuromuscular disease, creatinine clearance <30 ml/min, current participation in another research study, unable to understand and comply with protocol or to give written informed consent, contraindication to general anesthesia.

Electrophysiologic Procedure

Right and left femoral vessels were cannulated under general anesthesia. Arterial pressure was monitored continuously via the right radial artery. Transesophageal echocardiography (TEE) was performed to assess the appearance of the cardiac chambers, interatrial septum, LAA and PVs. A decapolar catheter was advanced to the coronary sinus and the left atrium was entered through double transseptal punctures, via the right femoral vein, under TEE and fluoroscopic guidance.
On crossing the atrial septum, intravenous unfractionated heparin (100 U/kg) was administered, with further boluses (20-50 U/kg) if necessary, to target an activated clotting time (ACT) of 300-350 seconds.