Catheter ablation of paroxysmal atrial fibrillation (AF) via pulmonary vein isolation (PVI) is highly effective. In contrast, in the majority of those with persistent AF, particularly if longstanding or associated with structural heart disease, PVI is crucial but alone is often insufficient for long-term maintenance of sinus rhythm. Ablation of complex fractionated electrograms (CFE), which may contribute toward—or reflect severity of—the atrial substrate, has shown variable benefit in randomized studies. Linear lesions at the left atrial (LA) roof and lateral mitral isthmus can also improve outcomes. Combining these approaches seems beneficial, although the optimal ablative strategies and order of their application remain uncertain.

Clinical Perspective on p 768

In patients with structurally normal hearts, PVI reduces remote LA CFE. Experimental and clinical models suggest that, unlike the reversible electric remodelling associated with atrial tachy-myopathy or lone AF, where remote CFE reduction might be explained by acute electric remodelling, a more advanced atrial substrate is seen in heart failure (HF) with evidence of structural remodelling, including dilatation and fibrosis, which are not acutely reversible. In the latter population, the effect of PVI and linear lesions on CFE remote from ablation sites is not known.

We sought to investigate the biatrial impact of stepwise ablation on CFE in patients with advanced atrial substrate of persistent AF and HF, and to assess factors influencing clinical outcome of catheter ablation in this challenging population.

Methods

Patient Population

Patients were recruited from the Ablation versus Rate Control for persistent atrial fibrillation in Heart Failure (ARC–HF) trial (ClinicalTrials.gov, NCT00878384). All had symptomatic persistent AF, without prior ablation, and left ventricular ejection fraction ≤35%. All patients gave written informed consent for the study, which was approved by the local clinical research ethics committee.

Electrophysiology Procedure

Procedures were performed on continuous oral anticoagulation (bridging low-molecular-weight heparin pre-2011). Under general anesthesia, transesophageal echocardiography ruled out intracardiac thrombus and guided transseptal puncture. Patients were heparinized to activated clotting time >300 seconds. The following...
Catheter Ablation Protocol

Antral PVI was performed in ipsilateral pairs, with carina ablation when necessary, and reisolation performed if required prior to all subsequent CFE maps. Linear ablation was performed at the roof between the venous isolation lines and at the lateral mitral isthmus between the left inferior pulmonary vein and the mitral valve annulus. The subsequent LA CFE map was used to guide ablation of CFE, with an end point of organization/ablation of local electrograms at all CFE sites except at the LAA (avoiding inadvertent isolation). If AF persisted, direct current cardioversion was performed after final CFE maps. If atrial tachycardia occurred, the protocol was terminated and the tachycardia mapped and ablated. In sinus rhythm, PVI was reassessed and realigned if necessary with the end point of entrance block. Bidirectional mitral and roof line block was assessed by differential pacing from the LAA, coronary sinus, and posterior wall; the presence of a blocked line immediately after cardioversion was defined as primary block. Further ablation was performed at incomplete lines, and then at the cavotricuspid isthmus, to achieve bidirectional block.

Analysis of CFE Maps

Each map was analyzed for CFE coverage. Using the surface marker function, all contiguous zones of CFE were annotated and the areas enclosed defined as CFE area. All LA CFE maps were superimposed on the geometry recorded immediately after linear lesions (Figure 2). The denominator LA area excluded the PVI encirclements and 5 mm from PVI and linear lesions, aiming to assess the effect of these lesions only on remote CFE. The final (post-CFE ablation) map assessed direct impact of ablation on residual LA CFE. In order to assess the remote effect of ablation on the RA, the RA CFE maps were superimposed on the final RA geometry; any LA ablation lesions within 10 mm of the RA surface were projected and these areas excluded to minimize confounding impact of transmural LA lesions (Figure 3).

In order to categorize CFE distribution, the LA was divided into 3 segments as described elsewhere, namely anterior, posterior (each defined by a superior limit of the roof line and lateral limit of the mitral isthmus line), and appendage (Figure 4A). The RA was similarly segmented into lateral, septal (split at the midline of the tricuspid annulus), and appendage (Figure 4B).

Statistical Analysis

Continuous data are presented as mean±SD and categorical data as frequency/percentage. Median/interquartile range is also presented for baseline variables and nonnormally distributed data. CFE area was analyzed by absolute and percentage coverage of atrial surface. To account for multiple measurements, regression with robust variances was performed using individual patients as a cluster variable, allowing relaxing of the assumption of independence within clusters. Stepwise change in CFE area and CL was analyzed by paired t test, using a Bonferroni correction to account for multiple comparisons. Linear regression was performed to assess factors associated with baseline CFE area (age, sex, AFCL, HF etiology, amiodarone, LA diameter, AF duration, and left ventricular ejection fraction), reduction of remote RA CFE area (adding radiofrequency duration), reduction of remote LA CFE area by PVI and linear lesions (adding primary linear block). Logistic regression was performed to assess predictors of AF termination. Pearson correlations were performed between changes in CL and CFE. Arrhythmia-free survival was assessed by Kaplan–Meier technique and Cox regression used to assess influencing factors. Analysis was performed within Stata for Windows. Two-sided P values <0.05 were regarded as significant.
Follow-Up
All antiarrhythmics except nonsotalol β-blockers were discontinued postablation, unless indicated for ventricular arrhythmia. Patients were followed up at 3, 6, and 12 months, routinely 6-monthly thereafter, and additionally for symptomatic recurrence. Forty-eight-hour Holter recordings, and device interrogation where possible, were performed at 6 and 12 months and ECG at subsequent follow-ups. Arrhythmia recurrence was defined as documented AF or atrial tachycardia >30 seconds after a 2-month blanking period.

Results
A total of 30 patients were studied, comprising consecutive patients from the ablation arm of the ARC–HF study13 (n=24; a 25th with incomplete mapping data was excluded) and those originally allocated to rate–control who subsequently underwent ablation after completing trial follow-up (n=6). Baseline patient characteristics are summarized in Table 1. HF etiology was ischemic in 12 patients (40%), with 3 postviral, 1 familial, 1 postalcohol, and the remainder idiopathic. Eleven patients had mild mitral regurgitation, 4 mild moderate, and none severe.

Catheter Ablation Procedure
Total procedural duration was 331±55 minutes, fluoroscopy time 79±18 minutes, and total radiofrequency ablation time precardioversion was 82±19 minutes (PVI 46±17 minutes; roof 3.3±1.7 minutes, mitral isthmus 4.0±2.3 minutes, CFE 12.1±7.7 minutes). Postcardioversion, primary roof block was present in 26/30 patients, the remaining 4 being blocked after further ablation (2.3±1.4 minutes). There was primary mitral block in 11/30 patients, and further ablation (6.6±3.5 minutes) in the remainder (including epicardially via the coronary sinus in 15) achieved block in 28/30 (93%). Cavotricuspid isthmus ablation (8.8±4.4 minutes) was performed in 28/30 patients, achieving bidirectional block in 27/28 (96%).

AF Termination
Termination of AF was observed in 6 cases. In 2, this occurred just prior to CFE ablation; roof-dependent atrial tachycardias were mapped and ablated to sinus rhythm. In 4, AF termination occurred during CFE ablation, 2 into sustained atrial tachycardia (perimital and focal—both successfully ablated), and 2 via transient organization then sinus rhythm. Considering baseline CL, overall CL prolongation prior to termination,
CFE area, LA size, primary linear lesion block, radiofrequency time, age, and AF history, there were no identifiable predictors of AF termination.

Mapping Procedure
A total of 168 CFE maps were acquired (Figure 1), constituting 114 LA maps (479±99 points per map) and 54 RA maps (373±96 points per map). The number of points per map did not differ significantly between baseline and subsequent LA (P=0.18) and RA (P=0.89) maps. Adjusted voltage detection threshold was 0.097±0.029 mV. The total surface area included for sequential CFE area analysis was 117±24 cm² in the LA (total LA surface 213±43 cm², 96±25 cm² excluded by PVI/linear lesions) and 136±33 cm² in the RA. Total LA CFE area, before exclusion of PVI/linear lesion zones, was 20.4±12.3 cm².

Impact of Catheter Ablation on CFE Area
At baseline, LA CFE area was 18.3±12.0 cm² (16.2±10.6% of the analyzed LA surface) comprising 7.9±6.0 cm² (6.8±5.1%) anteriorly, 6.6±5.8 cm² (5.9±5.3%) posteriorly, and 3.8±4.1 cm² (3.5±3.8%) in the LAA. After PVI, there was a reduction in CFE area to 10.2±7.1 cm² (9.0±6.6%; P<0.001 versus baseline), comprising 4.5±4.0 cm² (3.8±3.2%; P<0.001) anteriorly, 2.8±3.2 cm² (2.6±3.0%; P<0.001) posteriorly, and 2.8±2.5 cm² (2.5±2.3%; P=0.32) in the LAA. After addition of linear lesions and compared with post-PVI analysis, total LA CFE area had further reduced to 7.7±6.5 cm² (6.9±5.9%; P=0.06), comprising 4.2±4.2 cm² (3.7±3.7%; P=1.0) anteriorly, 1.7±2.8 cm² (1.6±2.6%; P=0.02) posteriorly, and 1.7±1.8 cm² (1.6±1.7%; P=0.04) in the LAA (Figure 5A).

As expected, direct CFE ablation significantly reduced final LA CFE area, compared with postlinear ablation analysis, to 3.1±3.5 cm² (2.8±3.0%; P=0.002), comprising 1.4±2.0

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics (N=30)</th>
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<td>Sex, men/women</td>
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<td>History of AF, mo</td>
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<td>Angiotensin/aldosterone-blockade</td>
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<tr>
<td>Amiodarone</td>
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<td>Implanted device (of which CRT)</td>
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AF indicates atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; IQR, interquartile range; LA, left atrium; and LV, left ventricular.
cm² (1.1±1.6%; P<0.001) anteriorly, 0.2±0.9 cm² (0.2±0.8%; P=0.01) posteriorly, and 1.6±2.1 cm² (1.5±2.1%; P=1.0) in the LAA.

At baseline, RA CFE area was 25.9±14.1 cm² (19.2±10.3% of the total RA surface), comprising 9.6±6.8 cm² (7.2±4.9%) laterally, 10.1±7.2 cm² (7.7±5.9%) septally, and 6.2±5.8 cm² (4.3±3.8%) in RAA. Final RA CFE area after LA ablation was reduced to 12.9±11.8 cm² (9.9±7.8%; P<0.001), comprising 7.0±7.1 cm² (5.6±5.3%; P=0.03) laterally, 2.5±2.8 cm² (2.0±2.1%; P<0.001) septally, and 3.6±3.9 cm² (2.5±2.6%; P=0.01) in the RAA (Figure 5B).

Impact of Catheter Ablation on AF Cycle Length
Analyzing all 3 components of ablation, LAA CL prolonged by 5.9 ms (95% confidence interval [CI], 3.4–8.4; P<0.001) and RAA CL by 3.2 ms (95% CI, 0.6–5.8; P=0.02) per step. LAA CL at baseline was 161±28 ms, prolonging to 170±37 ms after PVI (P=0.01), 174±34 ms after linear ablation (P=0.46 versus post-PVI), and 180±42 ms after CFE ablation (P=0.04 versus postlinear). RAA CL was lengthened from 167±33 ms at baseline to 175±33 ms after PVI (P=0.02), remained 174±30 ms after linear ablation (P=0.88 versus post-PVI), and prolonged to 179±41 ms after CFE ablation (P=0.03 versus postlinear). Hence biastral CL prolonged significantly after PVI and CFE ablation, but was not impacted independently by linear ablation. Change in CL did not significantly correlate with change in CFE area (R=0.21 in RA, P=0.35; for sequential LA maps, R=0.08–0.29, P=0.12–0.91).

Predictors of Baseline CFE Area
In multivariable analysis, only nonischemic etiology was a risk factor for higher baseline RA percentage CFE area (P=0.002; coefficient 11.2 cm²; 95% CI, 4.5–17.9). Higher LA percentage CFE area was only associated with shorter LAA CL (P=0.03; coefficient −0.084; 95% CI, −0.161 to −0.008).

Predictors of CFE Area Reduction After PVI and Linear Lesions
After correction for baseline remote CFE area, the reduction in CFE by PVI was independent of any identifiable variable. The reduction in CFE after linear lesions was greater in those with primary mitral block (P=0.02; coefficient −2.75 cm²; 95% CI, −5.13 to −0.39); primary roof block had no significant influence (P=0.17).

Clinical Outcome
After a single ablation procedure, at 494±223 days follow-up, 19/30 patients (63%) were free of atrial arrhythmias. Of the 11 patients with recurrence, 3 had AF and 8 had atrial tachycardia. Arrhythmia-free survival was 71.8% (95% CI, 51.3–84.8) at 1 year, off antiarrhythmic drugs, after a single procedure. The presence of unblocked linear lesions was the only predictor of arrhythmia recurrence in multivariable analysis (Table 2). No patient with procedural AF termination had recurrence within the follow-up period. Three patients died of progressive HF during follow-up at 1, 11, and 14 months; none had documented recurrent atrial arrhythmia.

Discussion
The main finding of this study is that in this human model of advanced atrial substrate—persistent AF and HF, LA CFE area was progressively reduced at remote sites following PVI and linear ablation. Furthermore, RA CFE area was reduced after ablation confined to the LA. In the LA, complete mitral isthmus block produced greater reduction of CFE area compared with incomplete block, and map-guided ablation of
residual (non-LAA) CFE after PVI and linear lesions eliminated the majority of CFE. The stepwise ablation strategy resulted in a high freedom from atrial arrhythmia following a single procedure, with atrial tachycardia the usual mode of recurrence. The presence of unblocked linear lesions at the end of the index procedure was the only independent predictor of arrhythmia recurrence.

Ablation of CFE

Since the initial data supporting CFE ablation to eradicate AF, investigators have targeted CFE alone, with PVI, or within stepwise strategies. However, randomized studies have produced conflicting results. In one, algorithm-guided CFE ablation post-PVI improved procedural success. In another, 2 hours of conventional CFE mapping and ablation provided no additional clinical benefit. Such discrepancies might relate to heterogeneity of CFE mapping techniques. Also, CFE mechanisms are incompletely understood; they may reflect slow conduction, localized reentry, wavelet collision, near high-frequency drivers, or locations of epicardial ganglionated plexi. Some of these mechanisms suggest fibrillation-maintaining source activity, whereas others suggest passive/bystander activation, a crucial distinction when judging their relevance as targets for catheter ablation.

It has been shown that PVI reduces fractionation at non-PV LA sites. More recently, Matsuo et al showed that in patients with mostly lone AF, linear lesions additionally reduced CFE at remote LA sites. These studies examined patients without significant structural heart disease and minimal atrial dilatation (mean 40–45 mm). In contrast, our study examined a model of more advanced atrial disease (LA dilatation and left ventricular dysfunction) and, uniquely, the impact of LA ablation on RA CFE, finding a significant reduction of remote CFE area and implying bystander activation, which may partly explain the lack of benefit from routine RA CFE ablation. If CFE represents sites of AF-maintaining (not bystander) activity, reduction of remote CFE by ablation in a lone-AF model could suggest acute electrophysiological remodelling. Our data, in a conceivably less reversible atrial substrate associated with chronic stretch and fibrosis, demonstrate that biventricular CFE are also reduced by remote ablation. Baseline CFE coverage was lower than the prior similar study among patients with a less advanced atrial substrate. This may be related to the CFE mapping methods used, although could reflect a substrate with more disparate islands of CFE, as similarly reported by Jadidi et al in patients with persistent AF and dilated atria, compared with the confluent CFE reported in lone AF in smaller atria. However, the relative reduction of remote CFE postablation was similar to earlier studies.

Linear Lesions

Although placement of complete linear lesions can be challenging, and incompleteness proarrhythmic, they improve long-term freedom from atrial arrhythmias. In addition to preventing macroreentrant tachycardia, compartmentalization may reduce both initiation and maintenance of AF. Allessie et al recently performed high-density epicardial mapping of persistent AF in humans, showing a substrate based on lines of block, rather than rotors or foci maintaining AF; with longitudinal dissociation facilitating multiple wavefronts. A recent study examined the impact of linear lesions on the atrial substrate based on the change in spectral components below the dominant frequency. These components were more prevalent in those with AF persistence, and complete linear lesions—but not PVI or CFE ablation—led to their reduction and elimination. Alteration of AF wavefront propagation and elimination of spectral components may explain

| Table 2. Cox-Regression Analysis Model for Atrial Arrhythmia-Free Survival After a Single Ablation Procedure (N=30) |
|---------------------------|-------------------|----------------|-------------------|
| Variable | Univariable | Multivariable |
| | HR | 95% CI | P Value | HR | 95% CI | P Value |
| Age/y | 0.99 | 0.93–1.06 | 0.77 | ... | ... | ... |
| Female | 0.60 | 0.16–2.31 | 0.46 | ... | ... | ... |
| LA size/5 mm | 1.80 | 1.09–2.97 | 0.022 | 1.66 | 0.93–2.98 | 0.09 |
| Implanted device | 2.02 | 0.60–6.84 | 0.26 | ... | ... | ... |
| Ischemic HF | 2.02 | 0.61–6.69 | 0.25 | ... | ... | ... |
| LV ejection fraction/5% | 0.90 | 0.63–1.29 | 0.56 | ... | ... | ... |
| AF, duration/mo | 1.01 | 0.98–1.04 | 0.41 | ... | ... | ... |
| Baseline LA CFE area/cm² | 1.01 | 0.96–1.07 | 0.62 | ... | ... | ... |
| Baseline RA CFE area/cm² | 1.00 | 0.96–1.05 | 0.85 | ... | ... | ... |
| Change in LAA CL/5 ms | 1.13 | 0.91–1.40 | 0.28 | ... | ... | ... |
| Change in LA CFE area/cm² | 0.92 | 0.09–9.80 | 0.95 | ... | ... | ... |
| AF termination | 0.03 | 0.00–11.44 | 0.25 | ... | ... | ... |
| Total RF, duration/10 min | 0.98 | 0.70–1.37 | 0.91 | ... | ... | ... |
| CFE RF duration/5 min | 1.09 | 0.71–1.66 | 0.69 | ... | ... | ... |
| Unblocked LL | 7.49 | 1.74–32.16 | 0.007 | 4.69 | 1.05–21.06 | 0.04 |

AF indicates atrial fibrillation; CFE, complex fractionated electrogram; CI, confidence interval; CL, cycle length; HF, heart failure; HR, hazard ratio; LA, left atrial; LAA, left atrial appendage; LL, linear lesion; LV, left ventricular; RA, right atrial; and RF, radiofrequency ablation.
our observed reduction in CFE and the favorable clinical outcome from robust linear lesions.

Sequence of Ablation in a Stepwise Approach

The ideal ablation strategy for persistent AF remains uncertain. Stepwise ablation, including PVI, CFE targeting, and linear lesions, can lead to favorable outcomes.\textsuperscript{7,8} If one intends to ablate CFE, our data support following PVI with linear lesions to minimize unnecessary CFE ablation,\textsuperscript{21} which itself may be proarrhythmic.\textsuperscript{26} Some CFE may facilitate ongoing AF;\textsuperscript{5} in our study, ablation of residual LA CFE after linear ablation prolonged AF CL and terminated AF in a handful of cases.

Procedural Outcome

The high single-procedure success mirrors that reported after similarly extensive ablation,\textsuperscript{9} although a smaller proportion of our patients had procedural AF termination. AF termination showed a trend toward predicting improved outcome in our cohort, but termination was not necessary for long-term success in the majority. The long procedure times inherent to our mapping and ablation protocol provided a long waiting time after PVI and linear lesions, which possibly contributed to the improved outcome.\textsuperscript{27} Prior failure of antiarrhythmic drugs or direct current cardioversion (present in only a third and half, respectively) were not inclusion criteria for the study. Hence, the AF in this population might have been less resilient than that in previous studies.

Limitations

This study has several limitations. The detection threshold was investigator-customized and fixed for each patient; thus, atrial CFE coverage may not be comparable to prior studies, and it is possible that some very-low-voltage CFE were missed. To minimize procedural duration, we did not acquire multiple RA CFE maps and hence cannot comment on the component effects of stepwise ablation on the RA CFE area. To minimize arrhythmia recurrence in this challenging population, we applied all contemporary ablation strategies rather than comparing them; hence, component impact on outcome is uncertain; however, the ongoing Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR-AF) II study (ClinicalTrials.gov, NCT01203748) is investigating this. The small number of patients with unblocked lines after ablation limits interpretation of impact on outcome. Although the study complied with the minimal ECG monitoring recommended by the HRS/EHRA/ECAS 2007/2012 consensus statements, silent AF episodes may have been missed in those without implanted devices. However, sinus rhythm at multiple visits suggests significantly reduced arrhythmia burden postsustained AF ablation.

Conclusions

In patients with persistent AF associated with left ventricular systolic dysfunction, high-density contact mapping revealed that PVI and linear lesions each had a significant effect in reducing LA fractionation at sites remote from ablation. LA ablation also led to a reduction in RA fractionation. A significant proportion of the CFE seen in the untreated atrium in this model of advanced atrial substrate was thus abolished by ablation at remote sites, which could suggest that at least some CFE represent incident activation rather than source activity. Completeness of linear lesions was associated with both greater CFE reduction and improved procedural outcome. Targeting CFE after PVI and linear lesions may minimize unnecessary collateral damage to atrial myocardium, and this ablation strategy was associated with a low rate of AF recurrence.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Catheter ablation of persistent atrial fibrillation remains challenging, and the optimal strategy has yet to be fully defined. The coexistence of structural heart disease, including heart failure and atrial dilatation, can make ablation less effective. However, there has been a slowly expanding accumulation of data suggesting ablation-based rhythm control is beneficial in such patients. There is evidence to support the application of pulmonary vein isolation, debulking or substrate-based ablation targeting abnormal or fractionated electrograms, linear lesions to compartmentalize and/or organize atrial activation, and combinations of these treatments in a stepwise fashion. However, the impact of all these ablation strategies on the atrial substrate remains poorly understood. This study provides new insights into the impact of stepwise ablation on the substrate in both atria, using high-density mapping in the context of atrial dilatation, mostly longstanding persistent atrial fibrillation, and left ventricular dysfunction. Pulmonary vein isolation and linear lesions were shown to reduce abnormal fractionation significantly at remote atrial sites in the left atrium, and left atrial ablation was shown to reduce remote right atrial fractionation. This may imply, first, that even advanced atrial disease might be amenable to reversal and, second, that widespread ablation of otherwise functionally abnormal sites, and the inherent potential for collateral damage or proarrhythmia, could be mechanically reduced using a stepwise approach to ablation strategy in advance. Further work, however, is still needed to identify individually tailored techniques and ablate only what needs ablating.
Impact of Stepwise Ablation on the Biatrial Substrate in Patients With Persistent Atrial Fibrillation and Heart Failure

David G. Jones, Shouvik K. Haldar, Julian W.E. Jarman, Sofian Johar, Wajid Hussain, Vias Markides and Tom Wong

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