Limited Ablation for Persistent Atrial Fibrillation Using Preprocedure Reverse Remodelling

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Abstract

Pulmonary vein isolation (PVI) has been demonstrated to be a highly effective treatment option for patients with paroxysmal atrial fibrillation (AF), but less effective for patients with persistent AF. The lower efficacy of PVI alone has been attributed to adverse atrial electrical and structural remodelling in the setting of AF. Strategies to improve efficacy of catheter ablation for persistent AF alter these pathophysiological characteristics of atrial tissue remodelling. Here we will review the physiology of atrial electrical remodelling observed during AF and evidence that it is reversible. Further, we will explore its uses to reduce the amount of atrial tissue that needs to be ablated to successfully treat patients with persistent AF.

Keywords

Atrial fibrillation, catheter ablation, reverse electrical remodelling, antiarrhythmic drug therapy

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Electrical Remodelling

Evidence Supporting Atrial Remodelling

The concept of electrical remodelling was first introduced in 1995 simultaneously by Wijffels et al.¹ and Morillo et al.² who demonstrated that once sustained atrial fibrillation (AF) was induced in goats, or rapid atrial pacing was performed in dogs, physiological changes occurred that favoured the maintenance of AF.³ This led to the concept that 'AF begets AF'.

Several aspects of the cellular and ion channel function changes that occur during persistent AF have been defined. These include:

- Reduced inward L-type Ca^{2+} current (I_{CaL}) by up to 70 %, reducing action potential duration (APD) and effective refractory period (ERP).^{4,5}
- Down-regulation of I_{CaL} to prevent Ca^{2+} overload during rapid atrial rates.⁶
- Upregulation of acetylcholine-dependent potassium current (I_{KACH}), which may contribute to shortening of the atrial ERP.
- Dysregulated connexin function, which plays an important role in electrical propagation during persistent AF.^{3,7}

The rapid rates of AF induce shortening of both the atrial ERP and APD.² Shortening of the ERP has been attributed to down-regulation of the L-type Ca^{2+} current (I_{CaL}) caused by Ca^{2+} accumulation within atrial myocytes.^{3,6} Spatial heterogeneity of ERP and conduction velocity also contribute to the pro-arrhythmic electrical changes observed in AF.⁸ The effects of atrial remodelling have been correlated with measurement of the P-wave duration on surface electrocardiogram (ECG) recordings.^{9,10} The shortened ERP reduces the wavelength of

atrial impulses that promotes wave break and multiple wavelet re-entry. Structural and mechanical atrial remodelling (which are beyond the scope of this review) along with electrical remodelling increase the frequency of ectopic and re-entrant arrhythmias and provide atrial tissue substrate that favours sustained re-entrant arrhythmias.^{6,11}

Evidence of Reverse Remodelling

The electrical components of atrial remodelling have been demonstrated to be reversible. Soon after studies revealed that AF begets AF, a study from Wijffels et al. recorded complete recovery of atrial ERP one week after cardioversion (goat model, AF duration 24 hours prior to cardioversion).^{1,12}

Animal experiments can directly measure various electrophysiological properties indicative of remodelling and reverse remodelling. This is more difficult in the clinical environment, especially without invasive procedures. However, surface ECG measurements of P-wave duration, including the maximum P-wave duration, P-wave dispersion, and high-resolution signal-averaged P-wave (SAPW) have proved to be accurate non-invasive reflections of atrial electrical remodelling.^{9,10,13–16}

For example, several studies have demonstrated that reverse electrical remodelling occurs in humans once sinus rhythm is restored. Using SAPW post-cardioversion, two studies revealed significant reduction in SAPW duration at one and three months post-cardioversion, but no reduction for patients who experienced recurrent AF.^{13,17} Another study demonstrated that patients who maintain sinus rhythm six months post-cardioversion have shorter P-wave duration compared

Figure 1: Six- and 12-month Outcome Post-pulmonary Vein Isolation

Patients with persistent atrial fibrillation who were pre-treated with dofetilide and then underwent pulmonary vein isolation (PVI) had a similar outcome at six and 12 months as patients with paroxysmal atrial fibrillation (AF) (76 % vs 80 % and 70 % vs 75 %, respectively, $P = NS$).²¹

with those with AF recurrence.¹⁸ Two studies evaluated invasive measures of electrical remodelling (ERP) four days and one week post-cardioversion.^{19,20} The studies revealed significantly decreased duration of SAPW and prolongation of atrial ERP, elegantly proving both the physiological phenomenon of atrial electrical reverse-remodelling and the fact that surface P-wave characteristics can be used as a non-invasive measure of atrial electrical remodelling.

Evidence Supporting Pre-ablation Procedure Atrial Remodelling

Based upon the physiological ability to promote reverse atrial electrical remodelling by restoring sinus rhythm, we and others have hypothesised that successful atrial remodelling by either cardioversion alone, or with the assistance of temporary antiarrhythmic drug (AAD) therapy, would facilitate the performance of pulmonary vein isolation (PVI) as the primary ablation strategy for patients with persistent AF.²¹⁻²⁴

Clinical Study Using Pre-ablation Antiarrhythmic Drug Therapy

Our study focused on consecutive patients with symptomatic, drug-refractory, persistent AF. To be included, patients had to be:

- In a persistent pattern of AF (≥ 7 days and ≤ 1 year) despite prior efforts at control using at least one class I or class III AAD;
- Free of contraindications to use dofetilide, a potent class III AAD.²¹

Patients underwent pre-treatment with dofetilide three months prior to ablation (with electrical cardioversion after six doses, if required), and the drug was continued one to three months after PVI ablation. Electrical remodelling was evaluated by measuring P-wave duration immediately after electrical cardioversion, and again at the time of presentation for PVI. If AF had recurred by the time the patient presented for ablation, P-wave duration was measured immediately after cardioversion to normal sinus rhythm. P-wave duration was measured in limb lead II, with ECGs in random order, by an observer blinded to the clinical outcome. The difference in P-wave duration (ΔP) between the ECG at the time of cardioversion and at the time of PVI was used as a measure of reverse remodelling.

We observed that more than 95 % of patients could be converted to nonpersistent AF or consistent sinus rhythm in the three-month interval preceding ablation.

The technique used for pulmonary vein catheter ablation isolation is described in detail in the original manuscript.²¹ Briefly, real-time 3D left atrial maps were constructed using a non-fluoroscopic navigation system (Carto®, Biosense-Webster Inc., CA, USA). A 20-pole catheter with distal ring configuration (Lasso Catheter®; Biosense-Webster Inc., CA, USA) was positioned within the ostium of each pulmonary vein. Radiofrequency catheter ablation was performed until all left atrial pulmonary vein connections were severed, as verified by the circumferential mapping catheter. All pulmonary vein connections were severed in each study patient. No patient underwent non-pulmonary vein ablation including linear lesions or targeting of complex fractionated atrial electrograms.

A control cohort of patients with symptomatic, paroxysmal AF who were referred for ablation and did not have prior pre-treatment of AF with AAD functioned as a control group for comparison purposes. P-wave durations at comparable points in time pre-ablation and at ablation were analysed. The treated persistent AF group was largely converted by dofetilide to paroxysmal AF. The control group was matched for age, gender, duration of AF, concomitant cardiovascular conditions, left atrial size and left ventricular function. Paroxysmal AF was defined as lasting less than seven days in duration and terminating spontaneously. Control patients underwent an identical ablation protocol. A sinus rhythm ECG recorded three months prior to ablation was compared with that recorded at ablation.

Patients were seen at one, three, six and 12 months or more frequently following PVI to assess for recurrence of AF. AF burden was evaluated using patient symptoms, 12-lead ECG, 24-hour Holter monitoring, and mobile cardiac outpatient telemetry. Specifically, after hospital discharge, each patient underwent a minimum of four weeks of mobile outpatient telemetry. At each office visit an ECG was recorded and an extended autotrigger transtelephonic monitor and/or 24-48 hour Holter recording was performed as needed to document asymptomatic AF episodes or to clarify symptoms. AAD treatment was discontinued three months post-ablation when complete freedom from AF was achieved.

A total of 71 consecutive patients with persistent AF were included. The median duration of the persistent AF episodes was six months. Overall, the group had mild left atrial dilatation and preserved left ventricular function. A median of one AAD had been ineffective in preventing recurrences of AF before initiation of dofetilide and the ablation procedure. Of the 71 study patients, 15 % required an early second PVI procedure. ECG analysis of the P-wave duration was performed on all patients at a median of 85 days prior to PVI and again at the time of PVI. Baseline characteristics for the 35 patients in the control cohort were not significantly different from the study group.

Efficacy of Dofetilide

All 71 patients in the treatment group tolerated AAD therapy with dofetilide (768 ± 291 mcg/day) preablation for a median of 85 days. During dofetilide initiation, all patients were converted to sinus rhythm. Sixty-nine (97 %) successfully transformed from persistent AF to either paroxysmal AF (56 patients, 81 %) or the AF was completely

suppressed (13 patients, 19 %). The remaining two patients (3 %) remained in persistent AF.

Response to PVI

All patients in both the treatment and control groups underwent successful catheter ablation isolation of all pulmonary vein connections. In the study of patients with persistent AF, 76 % were completely free of AF recurrence on no drug therapy at six months post-PVI, while 70 % were completely free of AF at 12 months post-PVI (responders). At six and 12 months, 24 % and 30 %, respectively, continued to have AF and required continued medical therapy or repeat ablation (nonresponders).

Among the control patients with paroxysmal AF, 80 % had complete response to PVI at six months and 75 % at 12 months. There was no significant difference in the 6- and 12-month PVI response in the study group versus the control group (see *Figure 1*). During the post-ablation period there was a single case of sustained left-sided atrial tachycardia, which occurred in the control paroxysmal AF group.

Of the 13 patients whose AF was completely suppressed with dofetilide pretreatment, 12 (92 %) had complete response to PVI at six months. Neither of the two patients who remained in persistent AF despite dofetilide pretreatment responded to PVI. Of those patients with persistent AF who responded to pretreatment with dofetilide, 75 % responded to PVI at six months.

Change in P-wave Duration

P-wave duration at baseline was significantly longer in the persistent AF group compared with the paroxysmal AF group ($p < 0.001$). Patients in the treatment group with persistent AF treated with dofetilide demonstrated a statistically significant reduction in the mean P-wave duration by the time they returned for PVI three months later (see *Figure 2*). In contrast, the cohort patients with paroxysmal AF who were not treated with AAD during the three months prior to PVI experienced no significant change in P-wave duration (see *Figure 2*). Patients with persistent AF who responded to PVI after pretreatment with dofetilide had a significantly greater decrease in P-wave duration in response to dofetilide (137.0 ± 23.1 to 116.7 ± 21.2 ms [20.3 ± 16.9 ms or 15 % decrease], $P < 0.001$) compared with nonresponders (132.9 ± 17.2 ms to 124.7 ± 16.6 ms [8.2 ± 12.4 ms or 6 % decrease], $P = 0.014$), (see *Figures 3 and 4*).

Predictors of Freedom from Recurrent AF Following Ablation

Age, gender, hypertension, left atrial size, duration of persistent AF episodes, duration of AF history, dose of dofetilide and clinical response (suppression vs. paroxysmal AF) to dofetilide all failed to predict a complete clinical response to PVI. A decrease in P-wave duration was the only significant predictor of clinical response to PVI (hazard ratio [HR] 0.94, confidence interval [CI] 0.90–0.98; $P = 0.009$) on univariate analysis. For each decrease in P-wave duration of 1 ms from baseline to ablation, there was a 6 % increase in the likelihood of a complete response to PVI. Similarly, on multivariate analysis a decrease in P-wave duration was again the only significant predictor of clinical response to PVI (HR 0.092, CI 0.86–0.98; $P = 0.007$).

Clinical Studies Using Cardioversion or Antiarrhythmic Drug Pre-ablation

Another study, based upon the same concept of reverse atrial electrical remodelling as a potential tool to limit the extent of catheter

Figure 2: Comparison of P-wave Duration Changes Over Time in Study and Control Patients

In patients with persistent atrial fibrillation (AF) dofetilide treatment was associated with a significant reduction in P-wave duration; in contrast, the P-wave duration remained unchanged in control patients with paroxysmal AF. At baseline, the P-wave duration was significantly longer in the study group when compared with the control group. PVI = pulmonary vein isolation.²¹

Figure 3: Comparison of Change in P-wave Duration Between Responders and Nonresponders

In patients with persistent atrial fibrillation, dofetilide therapy was associated with a significant reduction in P-wave duration in both responders and nonresponders. PVI = pulmonary vein isolation.²¹

ablation required for successful treatment of persistent AF, was published by Rivard et al. in 2012.²²

This two-group cohort study was conducted from 2007 through 2009 and included patients undergoing a first catheter ablation procedure for persistent and long-standing persistent AF. The study group consisted of 40 consecutive patients from three European centres who underwent electrical cardioversion one month prior to ablation. Patients who did not remain in sinus rhythm were excluded from the study, and all patients were required to have left atrial diameters ≤ 55 mm. These patients were retrospectively matched 1:1 with contemporary controls (for age, gender, duration of AF) with persistent AF in whom no attempt to restore sinus rhythm was made prior to ablation.

Radiofrequency catheter ablation was performed one month after cardioversion (for the study group), and after four weeks of therapeutic anticoagulation for both study arms. AAD therapy was discontinued

Figure 4: Comparison of Change in P-wave Duration Between Responders and Non-responders

Clinical response was assessed following pulmonary vein isolation (PVI) in patients with persistent atrial fibrillation who were treated with dofetilide. Responders demonstrated a significantly greater decrease in P-wave duration as compared with nonresponders (20.3 ± 16.9 ms vs 8.2 ± 12.4 ms, $P = 0.006$).²¹

Figure 5: Arrhythmia-free Survival After a Single Catheter Ablation Intervention

Number at risk in SR group	40	33	25	17	10	4	2
Number at risk in Control group	40	29	24	18	10	6	2

Kaplan-Meier recurrence-free survival rates are shown for patients having undergone a single catheter ablation procedure in the sinus rhythm (SR) and control groups.

five half-lives before the ablation procedure, with the exception of amiodarone. Ablation was performed during AF in all patients according to a sequential stepwise approach previously described in detail.²⁵ AF was induced by burst atrial pacing for patients who presented in sinus rhythm due to previous cardioversion. Briefly, left atrial antral PVI was performed using a 3.5 mm irrigated-tip catheter (ThermoCool™; Biosense Webster, Inc., CA, USA) and guided by a circular mapping catheter (LASSO; Biosense Webster, Inc., CA, USA). Next, electrogram-based ablation was performed at right atrial and/or left atrial sites demonstrating features of continuous electrical activity, complex rapid and fractionated electrograms, and a gradient of activation. If AF persisted after this step, linear ablation lesions were created across the left atrium roof between the superior pulmonary veins and then from the left inferior pulmonary vein to the mitral annulus. The endpoint was termination of AF during ablation. However, if AF persisted beyond these ablation lesions, electrical cardioversion was performed.

Patients were evaluated at one, three, six and 12 months post-ablation with 48-hour Holter monitoring performed at each visit.

Success was defined as the absence of AF or atrial tachycardia lasting 30 seconds or longer off AAD therapy.

Eighty patients were included in the study (40 in each arm). Both groups were similar with the exception of a slightly lower ejection fraction among patients in the control arm (63.9 ± 11.7 vs. 55.7 ± 14.9 , $P < 0.05$). AF cycle length was greater among patients who presented for ablation in sinus rhythm (i.e. induced AF in the treatment arm). Termination of AF occurred more frequently during ablation of patients in the treatment arm, with less extensive application of ablation and with less fluoroscopic exposure (see Table 1).

Clinical success without the use of AAD therapy was similar in both groups up to 36 months following ablation (see Figure 5). The need for repeat ablation was similar in both groups, and after the last procedure success rates off AAD therapy were 80 % in the treatment arm vs. 70 % in the control group ($P = 0.47$). Noninvasive measures of reverse remodelling were not performed.

The authors concluded that cardioversion and maintenance of sinus rhythm one month prior to ablation decreased the extent of ablation required to restore and maintain sinus rhythm without compromising efficacy.

Findings from two other independent studies support the hypothesis that pretreatment of persistent AF with AAD therapy and restoration of sinus rhythm improves efficacy of catheter ablation or at least identifies a subset of patients who are more likely to respond favourably to catheter ablation and thus may limit the extent of ablation lesions required for success.^{23, 24} Igarashi et al. studied 51 consecutive patients with drug-resistant persistent AF who underwent combined AAD therapy with both a class I and III AAD for greater than three months prior to catheter ablation.²³ AAD therapy consisted of a class III AAD (amiodarone or bepridil) plus a class I AAD (flecainide, aprindine, pilicainide or propafenone). Thirty three patients (65 %) converted to sinus rhythm during the three-month treatment period with dual AAD therapy (SR group). The sinus rhythm patients demonstrated evidence of mechanical remodelling such as improved left ventricular ejection fraction, reduced left atrial diameter, and reduced brain natriuretic peptide plasma levels. AAD therapy was discontinued five half-lives before the ablation, with the exception of amiodarone which was discontinued ≥ 2 weeks before catheter ablation.

All 51 patients underwent catheter ablation consisting of PVI and cavotricuspid isthmus ablation. Ten patients (28 %) from the sinus rhythm group and five patients (28 %) from the AF group ($p = ns$) required further ablation lesions including a left atrial roof line, superior vena cava isolation, and ablation of complex fractionated electrograms. Fourteen months following ablation, patients who converted to sinus rhythm during treatment with dual AAD therapy prior to ablation were significantly more likely to be in sinus rhythm following a single catheter ablation procedure (61 % vs 22 %; HR 2.62, 95 % CI 1.22–5.63; $p = 0.013$).

A retrospective case-control study of 82 patients with persistent AF examined outcomes according to those who underwent pretreatment with bepridil to restore sinus rhythm prior to ablation.²⁴ Fifteen of the 22 patients (68 %) treated with bepridil for a maximum of four months prior to ablation achieved sinus rhythm prior to ablation. AAD therapy

was discontinued at least three weeks prior to PVI ablation. Consecutive case-matched control patients ($n = 60$) underwent PVI ablation with the addition of left atrial linear ablation lesions if AF remained inducible. At the end of 18 ± 5 months off AAD therapy, the AF-free rate among patients successfully treated with bepridil who converted to sinus rhythm was 87 %, vs. 29 % for patients who failed to convert with AAD pretreatment. Seventy-two percent of case-matched control patients (not pretreated) remained in sinus rhythm (72 % vs 29 %, $p=0.02$). Conversion to sinus with bepridil identified a select group of patients with persistent AF who were more likely to respond to PVI. The question of whether restoration of sinus rhythm played a causative role (by reverse remodelling) in the long-term favourable outcome of this group was uncertain.

Discussion

Together, these studies confirm that:

- Pretreatment of patients with persistent AF to restore sinus rhythm prior to catheter ablation, regardless of whether this is accomplished by drug or simple cardioversion, identifies a group of patients who are more likely to respond favourably to PVI catheter ablation.
- Electrical remodelling plays a role in the maintenance of persistent AF.
- Restoration of sinus rhythm facilitates pre-ablation reverse remodelling to occur.
- Catheter ablation for patients with persistent AF may at least be less complicated and prolonged if electrical remodelling is allowed to occur first, and is likely more effective.

The physiological evidence for reverse remodelling is demonstrated by the shortening of the P-wave duration and the longer AF cycle length among patients converted first to sinus rhythm. One potential explanation for the difference between studies is the difference duration of sinus rhythm prior to AF ablation. It is possible that one month is insufficient time to allow for full electrical remodelling. Whether three months is adequate remains unanswered.

Limitations

The studies presented are non-randomised and relatively small. It is possible that by identifying patients who could remain in sinus rhythm (with dofetilide or after cardioversion alone or with other AAD therapy), a cohort of patients more likely to respond favourably to ablation was selected.²⁶ A larger multicentre trial is needed to confirm these findings and the long-term benefits of this approach. And finally, a randomised clinical trial is needed to definitively establish the value of the clinical strategy described in these manuscripts with alternative ablation techniques for persistent AF.

This paper is not intended to include a comprehensive review of the phenomenon of atrial electrical remodelling associated with AF. Rather, we have focused on aspects that have been demonstrated to be relevant to ablation of persistent AF and for which some clinical data exists. Reverse electrical remodelling begins within minutes to hours following cardioversion, whether cardioversion is performed electrically or pharmacologically. Cardioversion during catheter ablation of AF is often performed to evaluate efficacy if ablation lesions. But we know of no data that evaluate whether restoration of sinus rhythm by cardioversion during ablation affects outcome of catheter ablation of persistent AF. The effect on ablation outcome

of maintenance of sinus rhythm for less than one month prior to ablation of persistent AF remains unknown.

Practical Application of the Reverse Remodelling Concept

Catheter ablation for patients with symptomatic AF (paroxysmal or persistent) remains a long-term management strategy. Cardioversion with or without subsequent AAD therapy is often required acutely to alleviate severe symptoms and achieve adequate ventricular rate-control while a more definitive long-term treatment strategy is identified and then performed (e.g. linear lesion ablation strategy, ablation of autonomic ganglia, or rotor mapping/ablation). Even for patients with persistent AF who have only mild to moderate symptoms, elective cardioversion with or without AAD therapy may be viewed as a temporising intervention until a more definitive intervention such as catheter ablation may be viewed favourably by both the patient and physician. In addition to the benefits of atrial electrical remodelling, this period of time allows the patient time to consider the complex treatment options for persistent AF and confirm the symptom that was associated with AF. It also allows time for scheduling the catheter ablation which is resource-intensive and often must be scheduled weeks to months in advance.

Therefore, from a practical standpoint, many patients are already undergoing a period of reverse atrial electrical remodelling prior to catheter ablation of persistent AF, and the application of atrial reverse electrical remodelling may be considered a complementary tool to AF ablation strategies.

While our study utilised dofetilide to assist in maintenance of sinus rhythm prior to ablation of persistent AF, sinus rhythm is the essential component that allows electrical remodelling to occur, not the AAD.^{1,3,12,22} If dofetilide is not available or not appropriate for an individual patient, evidence suggests that the same benefit of preprocedural electrical remodelling would be achieved with other antiarrhythmic agents that effectively maintain predominant sinus rhythm.

Conclusions

AF, the most common heart rhythm disturbance, represents the end result of complex structural, electrical and mechanical changes of the atrial tissue. Early in the disease process, elimination of pulmonary vein triggers has been demonstrated to be effective therapy for many patients. However, as the disease process progresses, electrical and structural remodelling create conditions that favour continuation of AF.

Most ablation techniques for persistent AF are founded upon the theory that atrial tissue substrate modification, in addition to elimination of AF triggers, is required to improve ablation efficacy. Preprocedure electrical remodelling by restoration and maintenance of sinus rhythm one to three months prior to ablation for persistent AF offers an alternative strategy to improve ablation efficacy without extending the procedure duration and without exposing patients to the associated risks of prolonged procedures and extensive ablation lesions.

Randomised, controlled multicentre studies are needed to further characterise the effectiveness of preprocedure electrical remodelling prior to ablation of persistent AF and to clearly define the optimal duration of sinus rhythm required for electrical remodelling. ■

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