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Increase in organization index predicts atrial fibrillation termination with flecainide post-ablation: spectral analysis of intracardiac electrograms

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Aims

The mechanism of the action of flecainide in the termination of human atrial fibrillation (AF) is not fully understood. We studied the acute effects of flecainide on AF electrograms in the time and frequency domain to identify factors associated with AF termination.

Methods and results

Patients who were still in AF at the end of catheter ablation for AF were given intravenous flecainide. Dominant frequency (DF) and organization index (OI) were obtained by fast Fourier transform of electrograms from the coronary sinus catheter over 10 s in AF, before and after flecainide infusion. Mean AF cycle length (CL) was also calculated. Twenty-six patients were studied (16 paroxysmal AF and 10 persistent AF). Seven converted to sinus rhythm (SR) with flecainide. In all patients, mean CL increased from 211 ± 44 to 321 ± 85 ms ($P < 0.001$). Mean DF decreased from 5.2 ± 1.03 to 3.6 ± 1.04 Hz ($P < 0.001$). Mean OI was 0.33 ± 0.13 before and 0.32 ± 0.11 after flecainide ($P = 0.90$). Comparing patients who converted to SR with those who did not, OI post-flecainide was 0.41 ± 0.12 vs. 0.29 ± 0.10 ($P = 0.013$), and the relative change in OI was 29 ± 33 vs. $-3.9 \pm 27\%$ ($P = 0.016$), respectively. No significant difference was noted in the change in CL and DF in the two groups.

Conclusion

Increase in OI, independent of changes to CL and DF, appears critical to AF termination with flecainide. Increase in OI holds promise as a sensitive predictor of AF termination.

Keywords

Atrial fibrillation • Spectral analysis • Flecainide

Introduction

Despite their widespread use in the treatment of atrial fibrillation (AF), the mechanism by which Class Ic anti-arrhythmic drugs terminate AF is not well understood. Early studies on the effects of flecainide¹ and propafenone² in canine AF suggested that the termination of AF was the result of a rate-dependent increase in atrial effective refractory period, which led to an overall increase in wavelength. However, more recent work on goat AF failed to show this relationship, but instead, found that widening of the temporal excitable gap to be consistently associated with AF

termination with flecainide, as was the case with several other anti-arrhythmic drugs used in the study.³ These studies utilized AF induction protocols in different animals, and also employed different methods of measuring atrial refractory periods, which make direct comparison difficult. Moreover, none of these proposed theories of pharmacological AF termination have been adequately tested in human AF, the mechanism of which remains incompletely understood.

Recent studies of intracardiac signals during catheter ablation for AF in humans have suggested that the prolongation of AF cycle length (CL)⁴ and increased organization⁵ of AF are associated

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with return to sinus rhythm (SR). Whether these observations can also reliably predict pharmacological termination of human AF is unclear. To gain greater understanding into the mechanism of AF termination using Class Ic anti-arrhythmic drugs, we used flecainide to assess its effect on time and frequency domain characteristics of human AF, using intracardiac signal analysis. We hypothesized that flecainide will prolong AF CL, reduce the dominant frequency (DF) of AF, as well as increase its organization prior to termination.

Methods

Patients who were given flecainide during catheter ablation for AF were studied. All documented AF during the ablation procedures were either spontaneous or already pre-existent. No programmed AF induction was carried out in any patient. Paroxysmal AF is defined as AF that terminates spontaneously within 7 days, whereas persistent AF is defined as AF which is sustained beyond 7 days or lasting less than 7 days but requiring pharmacological or electrical cardioversion. All anti-arrhythmic therapy was discontinued for more than five half-lives prior to the procedure.

Atrial fibrillation ablation was carried out using bilateral femoral venous access. Under fluoroscopic guidance, a deflectable decapolar catheter and a quadripolar catheter were positioned in the coronary sinus and His position, respectively. A circular pulmonary vein mapping catheter and a deflectable, irrigated tip ablation catheter were advanced into the left atrium after transseptal puncture. Standard segmental ostial pulmonary vein isolation alone ($n = 13$) was performed in patients with paroxysmal AF. More extensive ablation was carried out in patients with persistent AF or when paroxysmal AF failed to terminate with segmental ostial pulmonary vein isolation alone. This consisted of either segmental ostial pulmonary vein isolation with linear ablation, followed by complex fractionated electrogram ablation ($n = 10$), or wide area circumferential ablation followed by linear ablation ($n = 3$). In all cases, left atrial anatomical geometry was created using EnSite NavX™ electroanatomical mapping (St Jude Medical Inc., St Paul, MN, USA). Patients who remained in AF at the end of the ablation procedure (either in AF at the start or developed AF during ablation) were given flecainide. This was administered at a dose of 2 mg/kg body mass (maximum of 150 mg) as intravenous infusion over 10 min, followed by observation for 10 min for any change in cardiac rhythm.

Time and frequency domain analyses

Intra-cardiac electrograms were recorded on a 30–500 Hz filter with a sampling frequency of 1 kHz (Labsystem Pro, Bard Electrophysiology, Lowell, MA, USA). Time and frequency domain analyses were carried out offline. Analysis was carried out on bipolar AF electrograms recorded from the decapolar catheter in the coronary sinus at the end of catheter ablation for AF. All electrograms with good signal quality on the decapolar catheter were analysed. Readings were taken prior to flecainide infusion, as well as after the full dose of flecainide had been given. In the event of return to SR after flecainide infusion, electrograms just prior to rhythm change were analysed. Cycle length measurements were carried out using built-in autodetection software (Labsystem Pro) and also verified manually. Mean CL was calculated over a 10 s recording period. The same 10 s segment was exported and analysed using fast Fourier transform with a spectral resolution of 0.24 Hz (4096 points), after processing with a Hamming window. A 1024 point sliding window was used to give the mean DF and mean organization index (OI) of the signal. The DF is defined as the frequency with the tallest peak in the power spectrum,⁶

and OI was derived by dividing the area under the DF and its harmonics by the total power of the frequency spectrum.⁵

Statistical analysis

All continuous variables are expressed as mean \pm standard deviation. Normally distributed data were analysed using paired and unpaired Student's *t*-test as appropriate. Categorical data were analysed using χ^2 or Fisher's exact test. Logistic regression was carried out to identify independent predictors of outcome after flecainide infusion, and receiver operator characteristic analysis was used to evaluate the relevant parameter. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 26 patients were included in the study. Sixteen (62%) had paroxysmal AF and 10 (38%) had persistent AF. Four of the patients with paroxysmal AF were in AF at the start of the procedure, whereas the remaining 12 developed AF spontaneously during the procedure. All patients with persistent AF started the procedure in AF. Seven (27%) converted to SR with flecainide (6 paroxysmal AF, 1 persistent AF). Average time to cardioversion with flecainide was 252 ± 96 s after initiating the infusion. Taking all patients together, mean CL increased from 211 ± 44 to 321 ± 85 ms ($P < 0.001$) after flecainide. Mean DF decreased from 5.2 ± 1.03 to 3.6 ± 1.04 Hz ($P < 0.001$). The mean OI remained unchanged [0.33 ± 0.13 before and 0.32 ± 0.11 after flecainide ($P = 0.90$)]. The inverse of the DF ($1000/DF$) revealed a strong linear relationship with mean CL (Pearson correlation coefficient = 0.90, $P < 0.001$) (Figure 1). Representative examples of intracardiac recordings and frequency spectrum analysed for this study are shown in Figures 2 and 3. Figure 2 shows data on the electrocardiogram (ECG) (lead V1) and intracardiac electrograms before and after intravenous flecainide in a patient whose AF did not terminate with flecainide together with the corresponding spectral data from FFT analysis, whereas Figure 3 shows the

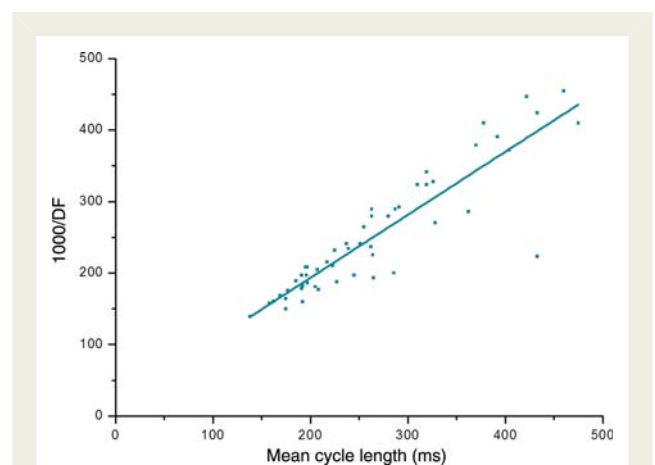


Figure 1 Plot of mean cycle length during atrial fibrillation and the inverse of corresponding dominant frequency ($1000/DF$) in all patients with and without intravenous flecainide showing a linear relationship between the two parameters (Pearson correlation coefficient 0.90, $P < 0.001$).

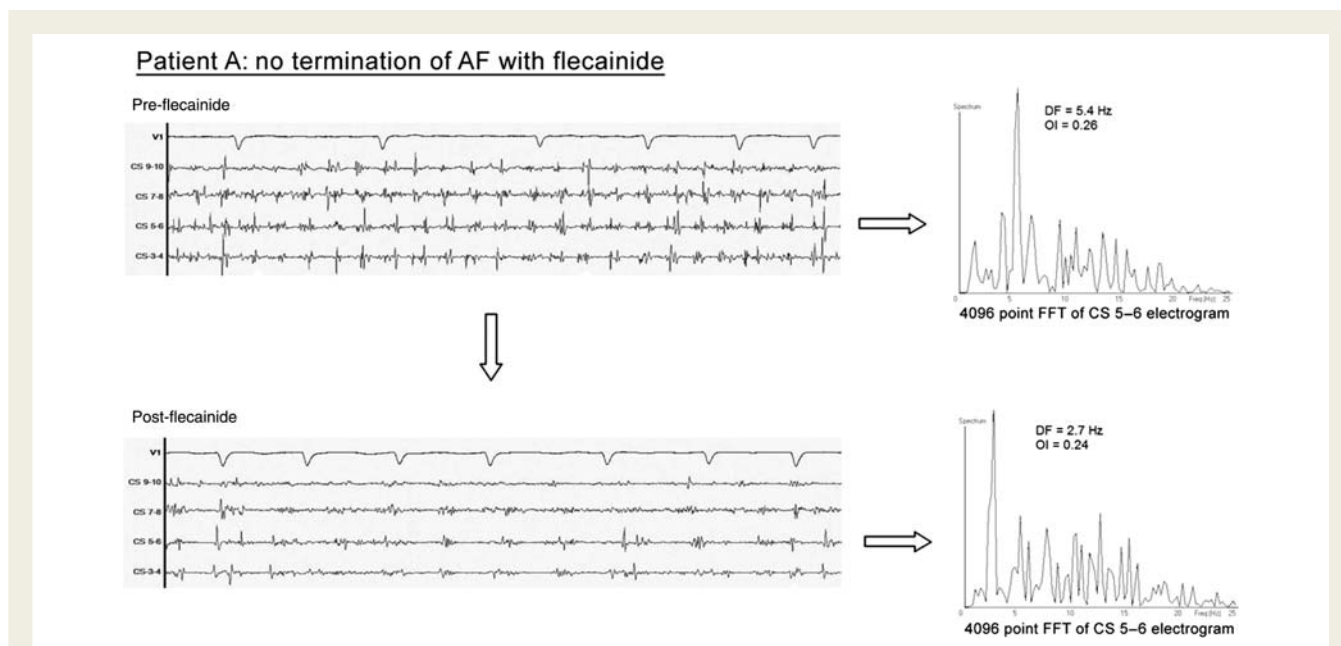


Figure 2 Typical example of a patient (Patient A) in whom atrial fibrillation did not terminate with intravenous flecainide. The left hand panels show electrocardiogram lead V1 and intracardiac electrograms before and after flecainide. The right-hand panels show the corresponding frequency spectra, with dominant frequency decreasing from 5.4 to 2.7 Hz, but organization index showed little change (0.26 pre- and 0.24 post-flecainide) with flecainide.

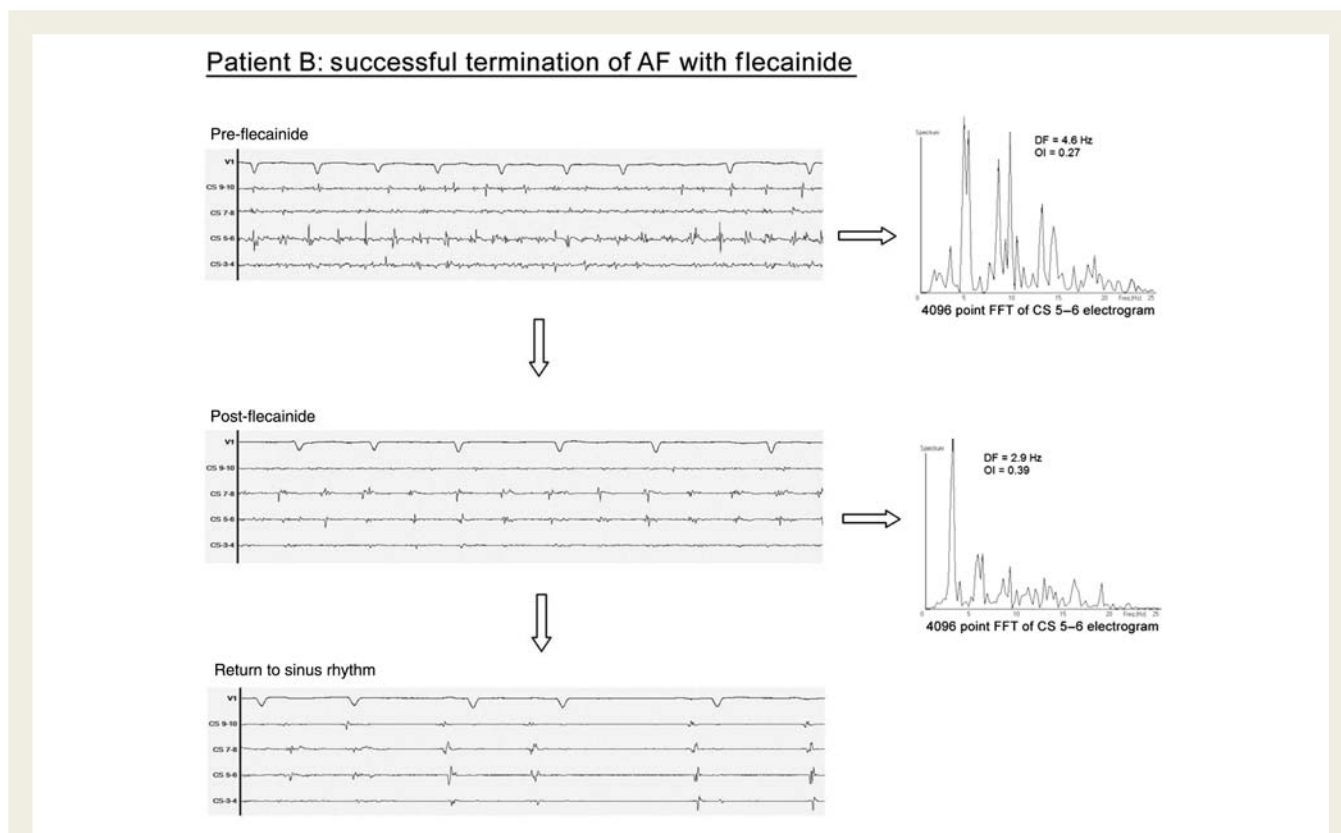


Figure 3 Typical example of a patient (Patient B) in whom atrial fibrillation terminated with intravenous flecainide. The left-hand panels show electrocardiogram lead V1 and intracardiac electrograms before and after flecainide and after returning to sinus rhythm. The right-hand panels show the corresponding frequency spectra with dominant frequency decreasing from 4.6 to 2.9 Hz and organization index increased from 0.27 to 0.39 before return to sinus rhythm.

Table 1 Patient characteristics

	Successful termination of AF with flecainide (n = 7)	Failed termination of AF with flecainide (n = 19)	P-value
Age	48 ± 9	55 ± 11	P = 0.14
Sex (male), n (%)	6 (86)	14 (74)	P = 0.65
Paroxysmal AF, n (%)	6 (86)	10 (53)	P = 0.19
Persistent AF, n (%)	1 (14)	9 (47)	
Hypertension, n (%)	4 (57)	8 (42)	P = 0.67
Ejection fraction (%)	52 ± 5	54 ± 3	P = 0.28
Left atrial dimension (cm) (parasternal measurement)	4.1 ± 0.6	4.3 ± 0.6	P = 0.66
Rhythm at the start of the procedure, n (%)			
SR	6 (86)	6 (32)	P = 0.026
AF	1 (14)	13 (68)	
Ablation strategy			
PVI alone	4	9	P = 0.53
PVI + CFE ablation	3	7	
WACA	0	3	
Total ablation times (s)	2963 ± 882	3424 ± 1809	P = 0.52
CL pre-flecainide	202 ± 52	214 ± 42	P = 0.53
CL post-flecainide	335 ± 90	316 ± 85	P = 0.61
Absolute change	134 ± 100	101 ± 71	P = 0.37
%Change in CL	76 ± 64	48 ± 34	P = 0.16
DF pre-flecainide	5.4 ± 1.4	5.1 ± 0.9	P = 0.59
DF post-flecainide	3.2 ± 0.89	3.8 ± 1.1	P = 0.20
Absolute change	-2.2 ± 1.7	-1.33 ± 1.0	P = 0.12
%Change in DF	-37 ± 24	-25 ± 19	P = 0.21
OI pre-flecainide	0.33 ± 0.11	0.32 ± 0.13	P = 0.90
OI post-flecainide	0.41 ± 0.12	0.29 ± 0.1	P = 0.013*
Absolute change	0.08 ± 0.11	-0.03 ± 0.1	P = 0.017*
%Change in OI	29 ± 33	-3.9 ± 27	P = 0.016*

PVI, pulmonary vein isolation (segmental ostial); CFE, complex fractionated electrograms; WACA, wide area circumferential ablation; CL, cycle length; DF, dominant frequency; OI, organization index.

*P < 0.05 considered significant.

same analysis in a patient whose AF converted to SR with flecainide.

Comparing patients who converted to SR after flecainide with those who remained in AF, OI post-flecainide was 0.41 ± 0.12 vs. 0.29 ± 0.10 ($P = 0.013$), and relative change in OI was 29 ± 33 vs. $-3.9 \pm 27\%$ ($P = 0.016$), respectively. No significant differences were noted in the mean CL and DF post-flecainide, and similarly, no significant differences were seen in the relative change in CL and DF in the two groups. Mean CL post-flecainide was 335 ± 90 vs. 315 ± 85 ms ($P = 0.61$), mean DF was 3.2 ± 0.9 vs. 3.8 ± 1.1 Hz ($P = 0.20$), relative change in CL was 76 ± 64 vs. $48 \pm 34\%$ ($P = 0.16$) and relative change in DF -37 ± 24 vs. $-25 \pm 19\%$ ($P = 0.21$), when comparing patients who returned to SR after flecainide with those who stayed in AF, respectively. There were no significant differences in the CL, DF, or OI between the two groups prior to flecainide administration. Detailed characteristics of the study patients can be found in Table 1. Logistic regression analysis identified that a greater relative increase in OI ($P = 0.04$), a higher OI post-flecainide ($P = 0.03$),

and SR at the start of procedure ($P = 0.03$) to be independently associated with successful reversion to SR with flecainide. Receiver operator characteristic curves indicate that an OI of >0.33 and a relative increase in OI of $>14.8\%$ independently have a 71% sensitivity and 79% specificity for identifying those who will return to SR after flecainide administration [area under curve 0.82 ($P = 0.01$) and 0.77 ($P = 0.03$), respectively].

Discussion

This study shows, using spectral analysis of intracardiac electrograms, that the mechanism of human AF termination by flecainide is critically preceded by organization of the arrhythmia, as reflected by an increase in OI. Although CL prolongation and corresponding reduction in DF occurred with flecainide administration, they did not predict return to SR. This suggests that an increase in the organization of AF is a more sensitive predictor of cardioversion to SR than the change in DF or CL.

Mechanism of atrial fibrillation termination with flecainide

According to the multiple wavelet hypothesis proposed by Moe and Abildskov,⁷ AF is the result of multiple wavelets of re-entrant circuits propagating throughout the atria. The relationship between re-entry and wavelength was first described by Mines⁸ and also subsequently by Lewis.⁹ Wavelength can be described as the minimal pathlength that supports re-entry. This has been formulated mathematically by Wiener and Rosenblueth,¹⁰ who showed that wavelength (WL) [defined as a product of refractory period (RP) and conduction velocity (CV): $WL = RP \times CV$] critically determined the likelihood of re-entry. The greater the wavelength, the smaller the number of re-entrant circuits the atria can contain, hence reducing the likelihood of AF being sustained. The use of wavelength as an index to predict susceptibility to atrial arrhythmia has been studied previously by Rensma *et al.*¹¹ and found to be predictive in 75% of cases, making it a useful way to assess anti-arrhythmic potential of drugs.

This concept has led to the question of how Class Ic anti-arrhythmic drugs, which block sodium channels and decrease conduction velocity without any apparent effect on refractory period, can result in the termination of AF. Wang *et al.*¹² examined the response of human atrial tissue to flecainide and found that it increased atrial action potential duration and refractoriness enhanced by the rapid rates typical of AF. In a separate study, Wang *et al.*¹ demonstrated in a dog vagal AF model that flecainide terminated AF by causing a tachycardia-dependent increase in atrial effective refractory period (to a greater extent than reduction in conduction velocity) which increased the wavelength. This same study also showed that flecainide progressively increased the size and reduced the number of re-entry circuits, as well as slowing atrial activation until AF terminated.

However, the theory that flecainide and Class Ic anti-arrhythmic drugs in general can influence wavelength changes has been put in question by other studies. Using a goat chronic AF model, Wijffels *et al.*³ found that Class I agents (flecainide and cibenzoline) actually shortened the wavelength of AF, and widening of the temporal excitable gap was the only finding associated with pharmacological cardioversion of AF. An earlier study on flecainide in humans¹³ also failed to show any significant effect on atrial refractoriness. Similarly, Katrakis *et al.*¹⁴ found no change in atrial effective refractory period with flecainide infusion and pacing at different CLs in human subjects.

Using a mathematical model of AF, Kneller *et al.*¹⁵ found that pure sodium channel blockade terminated AF despite reducing wavelength, and likely mechanisms include the enlargement of the core size of primary rotors, increasing meander and extinction at boundaries, and reduction in the number of wavelets.

Frequency domain analysis of atrial fibrillation

Using spectral analysis of canine AF, Everett *et al.*¹⁶ showed that high AF organization increased the efficacy of burst pace termination and also electrical cardioversion¹⁷ of AF.

Bollmann *et al.*¹⁸ studied the use of oral flecainide in patients with persistent AF by carrying out frequency spectrum analysis

on high-resolution surface ECG recordings. A lower fibrillatory frequency post-flecainide and smaller left atrial size were found to predict restoration of SR. Using a similar technique, Husser *et al.*¹⁹ carried out time-frequency analysis of surface ECG of AF to compare the effects of flecainide and amiodarone with baseline. A reduction in both fibrillatory rate (converted from DF) and also exponential decay of the frequency spectrum were seen after drug administration, with effects more apparent in the flecainide group. The authors suggested that the decrease in exponential decay, seen with both flecainide and amiodarone, reflected organization of AF and was analogous to an increase in OI.

Atrial fibrillation cycle length analysis

Atrial fibrillation CL is generally thought to reflect local atrial refractoriness.²⁰ However, assessing the exact mechanism of AF CL prolongation in the setting of flecainide administration is difficult as it is believed to have a use-dependent effect on atrial refractoriness and conduction velocity,^{1,12,21} both of which can result in an increase in AF CL. Biffi *et al.*²² studied induced AF in 10 patients with paroxysmal AF. The mean of 100 consecutive AF intervals (measured from endocardial electrograms) was increased by both flecainide and propafenone prior to AF termination in all the study patients. All 10 patients returned to SR within 10 min of drug administration. The authors also remarked that the extent of AF interval prolongation occurred to a greater extent with drugs than with that observed in self-terminating AF in a previous study,²³ also carried out by the same group.

Implication of findings

The mechanism of AF termination with sodium channel blockade remains poorly understood. Using spectral analysis, we have demonstrated, in human subjects, that AF CL prolonged and DF reduced uniformly after flecainide administration; however, this did not predict return to SR. Reversion to SR with flecainide was independently associated with a higher OI post-flecainide and also a greater relative rise in OI induced by flecainide, regardless of change in CL or DF. This suggests that the process of AF termination depends critically on an increase in the organization of the arrhythmia, possibly even more crucially so than slowing of atrial activation. This implies that increase in the organization of AF is likely to be a more sensitive predictor of return to SR than the change in DF or CL. Although other studies have shown AF CL prolongation with Class Ic anti-arrhythmics, none have used spectral analysis to quantify the organization of the rhythm and its relationship with return to SR in human AF.

A higher OI is a marker of greater regularity. The increase in OI seen in our study can be hypothesized to reflect a reduction in the number of re-entrant circuits or drivers, prior to AF termination. When coupled with the increase in AF CL and reduction in DF (and hence slowing of atrial activation rate), it results in conditions favourable for return to SR. An isolated increase in AF CL or reduction in DF alone, with no increase in organization, probably represents continued presence of multiple re-entrant circuits or drivers which reduces the likelihood of return to SR.

Limitations

Our study reflects the behaviour of the ablated left atrium. However, it is probably not dissimilar to the spectral characteristics of the unablated left atrium since ablation alone was not sufficient to achieve termination of AF in these patients, implying the continued presence of unaddressed drivers or substrate maintaining AF.

Using a catheter placed in the coronary sinus has the advantage of stability in terms of positioning, but we acknowledge that the electrograms recorded from this catheter are not directly from within the left atrium and do not fully assess the global spatiotemporal characteristics of AF. However, in the context of assessing CL and spectral characteristics of human AF, the utilization of coronary sinus electrograms alone for analysis is well described in published literature,^{4,5,24,25} and although it has its limitations, it seems to be an acceptable technique.

Though not achieving statistical significance, there appears to be a trend suggesting that CL and DF changes may be greater in those who returned to SR after flecainide than those who did not. Owing to the small sample size, the study is not powered to conclusively exclude any link in CL and DF changes with the likelihood of returning to SR, although it still supports the notion that increase in OI is a more sensitive indicator.

Conclusion

Our findings provide an insight into the controversial mechanism of human AF termination with Class Ic agents such as flecainide. The spectral characteristics observed in our study appear to support findings reported by researchers using canine AF¹ and mathematical AF models.¹⁵ Similarly, our findings also reflect observations from the termination of AF with catheter ablation,⁵ burst pacing,¹⁶ and electrical cardioversion,¹⁷ adding further weight to the evidence that increased spectral organization plays a crucial role in AF termination, regardless of the method used to achieve this. The OI of AF appears to be a useful tool to assess for the likelihood of AF termination and may be useful as a target for development of AF therapy. Larger studies into spectral organization of AF are needed to further define its significance in human AF.

Conflict of interest: none declared.

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