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Regional fractionation and dominant frequency in persistent atrial fibrillation: effects of left atrial ablation and evidence of spatial relationship

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Aims The aim was to study regional fractionation and dominant frequency (DF) to determine if any relationship exists between the two parameters and also to assess the impact of limited left atrial ablation.

Methods and results Patients undergoing catheter ablation of persistent AF using three-dimensional navigation were studied. Regional left atrial electrograms were analysed in the frequency domain by assessing DF and organization index (OI), and for degree of fractionation [using complex fractionated electrograms (CFE)-mean] before and after circumferential pulmonary vein and left atrial roof ablation. Twenty-three patients with persistent AF were studied. After ablation, global CFE-mean increased [100 ± 5 to 147 ± 11 ms ($P = 0.0003$)], DF decreased [6.1 ± 0.2 to 5.3 ± 0.2 Hz ($P = 0.0003$)], and OI was unchanged [0.27 ± 0.01 to 0.26 ± 0.02, ($P = 0.70$)]. Comparing sites close to and distant from ablation lines, percentage change in CFE-mean was 94 ± 10 vs. $37 \pm 6\%$ ($P < 0.0001$), DF change was -13 ± 3 vs. $-12 \pm 2\%$ ($P = 0.98$), and OI change was 3 ± 6 vs. $10 \pm 5\%$ ($P = 0.75$), respectively. There was modest correlation between CFE-mean and DF points prior to ablation ($r = -0.33$, $P < 0.0001$) which was reduced following left atrial ablation ($r = -0.24$, $P = 0.005$).

Conclusions Left atrial ablation reduces global left atrial DF and decreases the degree of fractionation. Complex fractionated electrograms-mean and DF appear to share only modest spatial correlation and are affected to different extents by ablation, suggesting that they are either separate entities or reflect different components of the same substrate.

Keywords Fractionation • Dominant frequency • Ablation • Atrial fibrillation

Introduction

Catheter ablation for persistent atrial fibrillation (AF) remains a challenging procedure and success rates vary significantly between different centres.[1] Repeat procedures to treat further arrhythmia are frequently required in a significant proportion of patients.

Addressing AF substrate in addition to triggers is key to achieving maintenance of sinus rhythm with catheter ablation of persistent AF. Potential substrate targets that have been described include autonomic nervous tissue such as ganglionated plexi[2,3] and sites with complex fractionated electrograms (CFE)[4], and high dominant frequency (DF).[5] It is not known whether the targeting of a specific substrate is superior to another nor is it clear if these substrates may be related in any way.

To gain better understanding of the characteristics of AF substrate, we carried out a study to examine regional DF (frequency domain substrate) and fractionation (time domain substrate) characteristics before and after catheter ablation, so as to study the effect of ablation and also to assess if there is any spatial relationship between the two parameters.

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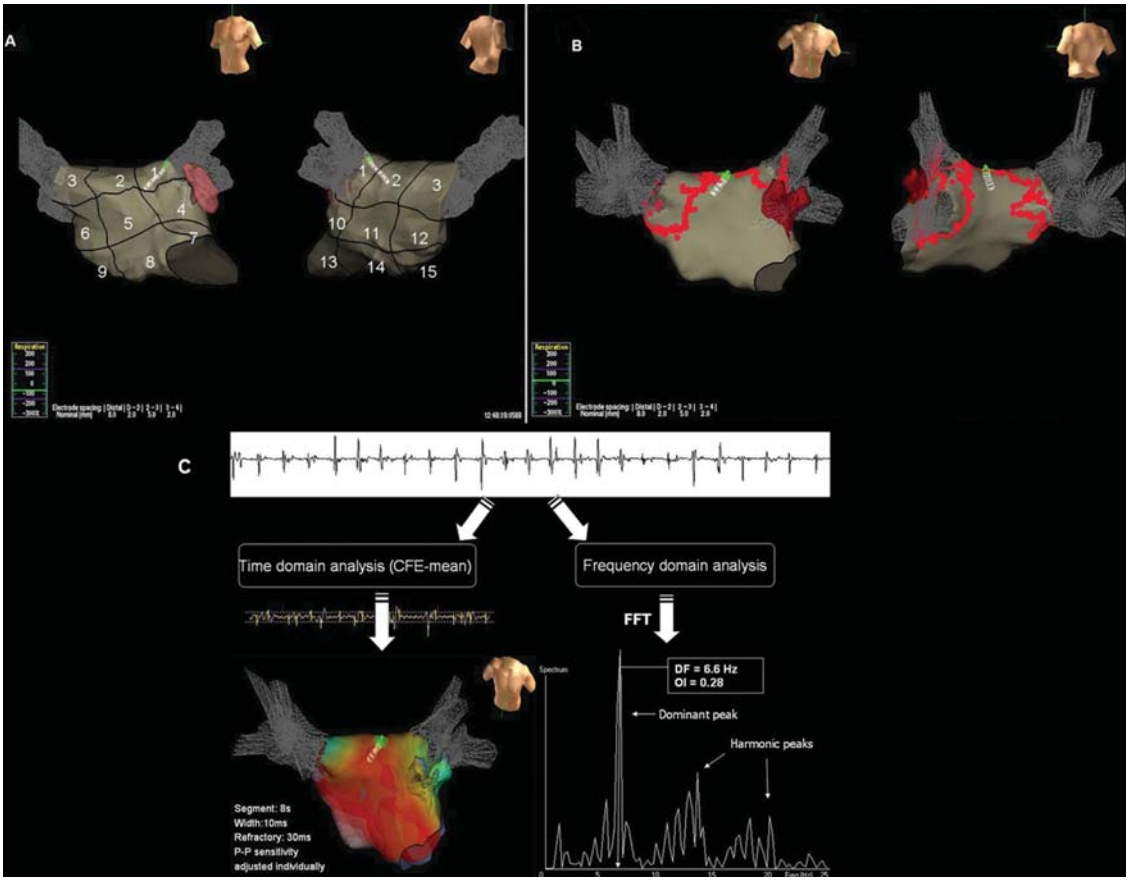

Figure 1 Left atrial mapping, ablation strategy, and electrogram analysis. The three-dimensional geometry of the left atrium is divided into 15 segments for atrial electrogram analysis. (*A*) A typical set of ablation lesions delivered for the purpose of the study, consisting of wide circumferential pulmonary vein and linear roof ablation are shown. (*B*) Electrograms were analysed using both time (complex fractionated electrograms-mean) and frequency domain to obtain dominant frequency and organization index. (*C*) Settings used to produce the complex fractionated electrograms-mean colour map on the left atrial geometry are displayed.

Methods

A consecutive series of patients undergoing catheter ablation of persistent AF for the first time were studied. Only patients in persistent AF at the start of the procedure were included. All anti-arrhythmic drugs apart from amiodarone were stopped for at least five half lives before the procedure. Once bilateral femoral venous access were achieved, a deflectable decapolar catheter and a quadripolar catheter were positioned in the coronary sinus and His position, respectively, under fluoroscopic guidance. A single transseptal puncture technique was utilized in all cases to gain access to the left atrium with the use of non-steerable transseptal sheath (LAMP 90, St Jude Medical, St Paul, MN, USA). Following this, a deflectable, variable loop circular pulmonary vein mapping catheter (Inquiry Optima, St Jude Medical, St Paul, MN, USA), and a 4 mm deflectable, irrigated tip ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA) were advanced into the LA with subsequent creation of left atrial geometry using a 3-dimensional navigation system (Ensite NavX^{TM}, St Jude Medical, St Paul, MN, USA).

Using the irrigated tip bipolar ablation catheter, point-by-point mapping of the left atrium was carried out according to a 15 segment grid superimposed on the three-dimensional left atrial geometry (which includes the pulmonary vein antrum/ostia, left atrial roof, septal, lateral, posterior, and anterior walls) before and after left atrial ablation. (*Figure 1A*) In all cases, left atrial ablation involved wide area circumferential ablation around ipsilateral pairs of pulmonary veins followed by linear roof ablation (*Figure 1B*). At least two samples of electrograms were collected at each segment and the trace with the best quality used for analysis. Once all signals required for the study had been obtained, further ablation strategy was left to the operator's preference. The end-point for completion of circumferential vein ablation while in AF was the electrical isolation of the pulmonary veins, as defined by the abolition of electrical signals on the circular mapping catheter when positioned within each pulmonary vein. Linear roof ablation was performed as a contiguous anatomical line, guided by the 3-dimensional atrial geometry. Conduction block across the roof line was confirmed at the end of the procedure when sinus rhythm was achieved, either through DC

cardioversion or by ablation. Electrical isolation of the pulmonary veins was also confirmed in sinus rhythm.

Analysis was done on electrograms over a period of 8 s of continuous recording at each grid segment: (i) in the time domain as degree of fractionation (expressed as 'CFE-mean') using automated detection software built into the navigation system to create a colour-coded CFE-mean map; and (ii) in the frequency domain with Fast Fourier Transform (FFT) to obtain regional DF and organization index (OI). Previous studies have suggested recording electrograms over at least 5 s to increase the accuracy of fractionation and DF assessment.[6,7] For the purpose of this study, we assessed degree of fractionation as a continuous variable by CFE-mean analysis to include all data between the range of 40 and 300 ms so as to include as wide a range of AF electrograms as possible. The CFE-mean is an average of the intervals between deflections on atrial electrograms which are detected based on a set of pre-defined criteria. Settings used for the generation of CFE-mean map on the navigation system were as follows: segment of 8 s, width 10 ms, refractory of 30 ms, and P–P sensitivity adjusted to adapt to the electrograms for each individual patient (between 0.05 and 0.12 mV) (*Figure 1C*).

All intra-cardiac electrograms were recorded with a 30–500 Hz band-pass filter with sampling frequency of 1 kHz and exported for spectral analysis. Fast Fourier Transform was carried out 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 OI of the signal. Dominant frequency is defined as the frequency with the tallest peak in the power spectrum[8,9] and OI was derived by dividing the area under the DF and its harmonics by the total power of the frequency spectrum (*Figure 1C*).[9,10]

All continuous variables are expressed as mean ± standard error of the mean. Normally distributed data were analysed using paired and unpaired Student's *t*-test as appropriate. Non-parametric data were analysed by Mann–Whitney or Wilcoxon signed rank test. Categorical data were analysed using χ^2 or Fisher's exact test. Correlation testing was carried out using Spearman's coefficient.

Results

A total of 600 wall segments of left atrial electrograms were collected from 23 patients recruited into the study, and 418 of these were used for analysis after discarding signals with poor signal to noise ratio (signal: noise amplitude of <2). Eight patients were on amiodarone at the time of the procedure. Post-ablation data were unavailable in six patients who converted to atrial flutter during ablation limited to the study protocol. Baseline characteristics of the study population are summarised in *Table 1*.

Global CFE-mean increased from 100 ± 5 to 147 ± 11 ms (mean ± SEM, $P = 0.0003$) and DF decreased from 6.1 ± 0.2 to 5.3 ± 0.2 Hz ($P = 0.0003$) after ablation. Mean OI was unchanged (0.27 ± 0.01 before and 0.26 ± 0.02 after ablation, $P = 0.70$).

In patients who were on amiodarone compared with those who were not, pre-ablation electrograms showed a non-significant trend towards a lower degree of fractionation (CFE-mean: 112 ± 12 vs. 93 ± 5 ms, $P = 0.10$) and higher degree of organization (OI: 0.29 ± 0.02 vs. 0.26 ± 0.01, $P = 0.27$) with a significantly lower DF (5.5 ± 0.1 vs. 6.5 ± 0.2 Hz, $P = 0.002$). Out of the eight patients on amiodarone, three (38%) converted to atrial flutter with ablation while three (20%) of 15 not on amiodarone did. This resulted in post-ablation AF electrograms being available for analysis in only five patients from the amiodarone group and in 12 not on amiodarone. Ablation caused similar significant increases in CFE-mean (77 ± 29 vs. 68 ± 10%, $P = 0.70$) and decreases in DF (12 ± 1 vs. 16 ± 3%, $P = 0.37$) regardless of whether patients were on amiodarone or not. Details of patients on amiodarone and otherwise with available pre- and post-ablation data are shown in *Table 2*.

Table 1 Patient characteristics of the study population

Patient characteristics ($n = 23$)	
Age (years)	57 ± 2
Male	19 (83%)
Duration of AF (months)	56 ± 7
Hypertension (number)	12 (52%)
Diabetes mellitus (number)	3 (13%)
EF (%)	48 ± 1
LA size (mm)	47 ± 1
Medication[a] (number of patients on)	
—ACE inhibitor/ARB	13
—Amiodarone	8
—Beta-blockers	16
—Calcium channel blockers	2
—Digoxin	2
—Statins	5

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.
[a]All anti-arrhythmic drugs (beta-blockers, calcium channel blockers, and digoxin) were stopped for at least five half lives before the procedure, with the exception of amiodarone which was continued.

Comparing across all 15 segments of the atrium, CFE-mean increased and DF reduced in all regions post-ablation. The three most fractionated sites (i.e. lowest CFE-mean) pre-ablation were localized to the septal and infero-posterior regions of the LA (regions 6, 9, and 14) which also appeared to contain the higher DF signals (see *Figure 2A* and *B*).

When comparing the three highest DF sites with the three most fractionated sites within each patient pre-ablation, one matching region occurred in 16 (70%) patients, two matching regions in three (13%), and three matching regions in none. The highest DF site corresponded with the lowest CFE-mean site in only two (9%) patients. However, highest DF sites and lowest CFE-mean sites occurred in adjacent regions in 12 (52%) patients.

At sites close to ablation lines (defined as those collected from points located within 5 mm of ablation lines) CFE-mean increased from 93 ± 5 to 173 ± 10 ms ($P < 0.0001$), DF decreased from 6.2 ± 0.2 to 5.3 ± 0.2 Hz ($P < 0.0001$), and OI change was 0.26 ± 0.01 to 0.25 ± 0.02 ($P = 0.60$) following ablation. At sites distant from ablation lines (defined as those collected from points located >5 mm from ablation lines) CFE-mean increased from 90 ± 3 to 122 ± 7 ms ($P < 0.0001$), DF decreased from

Table 2 Change in complex fractionated electrograms-mean, dominant frequency, and organization index with ablation—comparison of pre- and post-ablation data in patients who remained in atrial fibrillation (five out of eight on amiodarone and 12 out of 15 not on amiodarone)

		Pre-ablation	Post-ablation	*P* value
On amiodarone ($n = 5$)	CFE-mean (ms)	106 ± 12	176 ± 16	0.02
	DF (Hz)	5.6 ± 0.1	4.9 ± 0.1	0.008
	OI	0.31 ± 0.02	0.30 ± 0.04	0.65
Not on amiodarone ($n = 12$)	CFE-mean (ms)	89 ± 4	145 ± 11	0.0002
	DF (Hz)	6.5 ± 0.2	5.4 ± 0.3	0.003
	OI	0.24 ± 0.01	0.24 ± 0.01	0.41

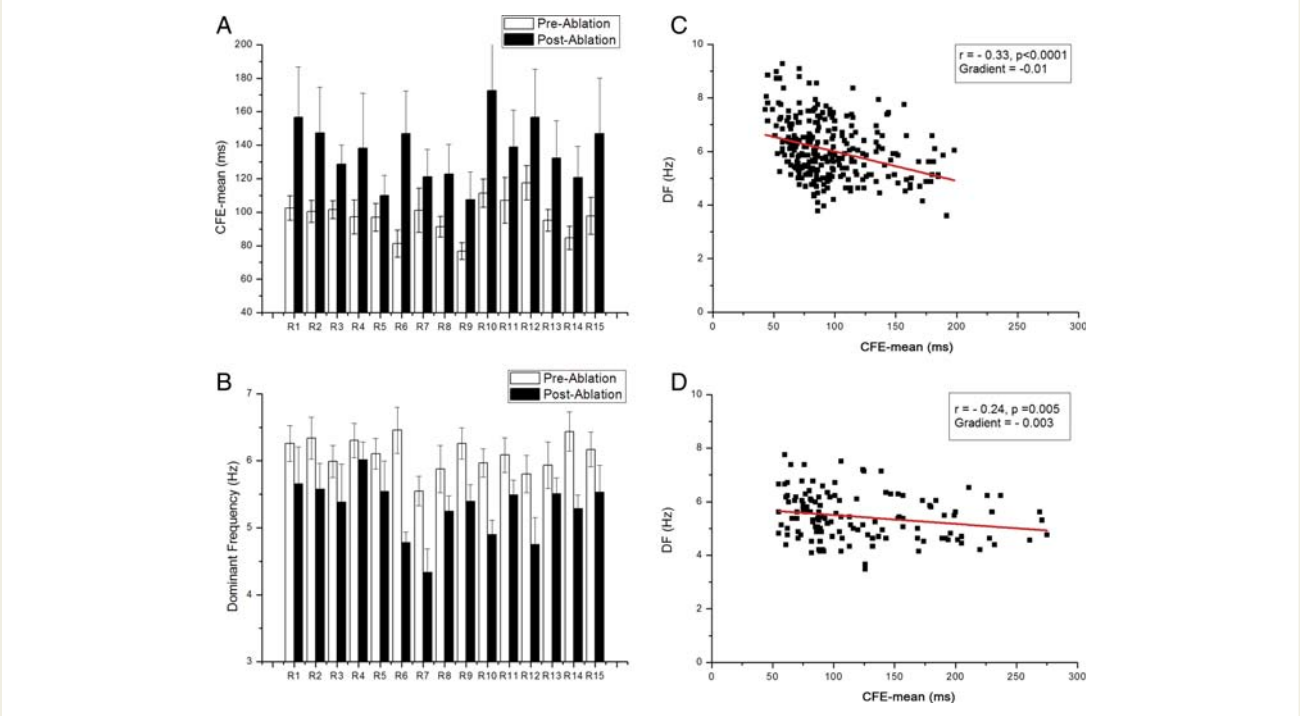

Figure 2 Regional complex fractionated electrograms -mean and dominant frequency , complex fractionated electrograms-mean vs. dominant frequency plots. Regional complex fractionated electrograms-mean (*A*) and dominant frequency (*B*) are plotted pre- and post-ablation across all 15 segments of the left atrium [Region 1 (R1) to Region 15 (R15) as displayed in *Figure 1*]. Pre- and post-ablation complex fractionated electrograms-mean vs. dominant frequency plots are shown in (*C*) and (*D*), respectively. There was a moderate degree of correlation which was further weakened post-ablation.

6.2 ± 0.1 to 5.4 ± 0.1 Hz ($P < 0.0001$), and OI change was 0.27 ± 0.01 to 0.26 ± 0.01 ($P = 0.81$) (*Table 3*).

Pre-ablation CFE-mean, DF, and OI were not significantly different between sites close to or distant from ablation lines [93 ± 5 vs. 90 ± 3 ms ($P = 0.62$), 6.2 ± 0.2 vs. 6.2 ± 0.1 Hz ($P = 0.96$), 0.26 ± 0.01 vs. 0.27 ± 0.01($P = 0.57$), respectively]. However, post-ablation CFE-mean was significantly greater at sites close to ablation lines (*Table 3*). On further comparing sites close to ablation lines with those distant from ablation lines, percentage change in CFE-mean was 94 ± 10 vs. 37 ± 6% ($P < 0.0001$), DF change was −13 ± 3 vs. −12 ± 2% ($P = 0.98$), OI change was 3 ± 6 vs. 10 ± 5% ($P = 0.75$), respectively.

There was modest correlation between CFE-mean and DF points prior to ablation ($r = -0.33$, $P < 0.0001$, see *Figure 2C*). The strength of this relationship was reduced following left atrial ablation ($r = -0.24$, $P = 0.005$, see *Figure 2D*).

Examples of regional CFE-mean and DF change in one of the study patients are shown in *Figure 3*.

Discussion

We have shown that left atrial ablation using the ablation strategy described above during persistent AF, reduces global left atrial DF and also decreases the degree of fractionation (seen as an increase

Table 3 Change in complex fractionated electrograms-mean, dominant frequency, and organization index between points close to (≤5 mm) and distant (>5 mm) from ablation lines

		Pre-ablation	Post-ablation	*P* value
Points close to ablation lines[a]	CFE-mean (ms)	93 ± 5	173 ± 10*	<0.0001
	DF (Hz)	6.2 ± 0.2	5.3 ± 0.2**	<0.0001
	OI	0.26 ± 0.01	0.25 ± 0.02***	0.60
Points distant from ablation lines[b]	CFE-mean (ms)	90 ± 3	122 ± 7*	<0.0001
	DF (Hz)	6.2 ± 0.1	5.4 ± 0.1*	<0.0001
	OI	0.27 ± 0.01	0.26 ± 0.01***	0.81

[a]Points close to ablation lines ($n = 53$, typically at atrial segments 1, 2, 3, 6, 10, and 12).
[b]Points distant from ablation lines ($n = 115$, typically at atrial segments 4, 5, 7, 8, 9, 11, 13, 14, and 15).
*$P = 0.0001$, **$P = 0.66$, ***$P = 0.66$.

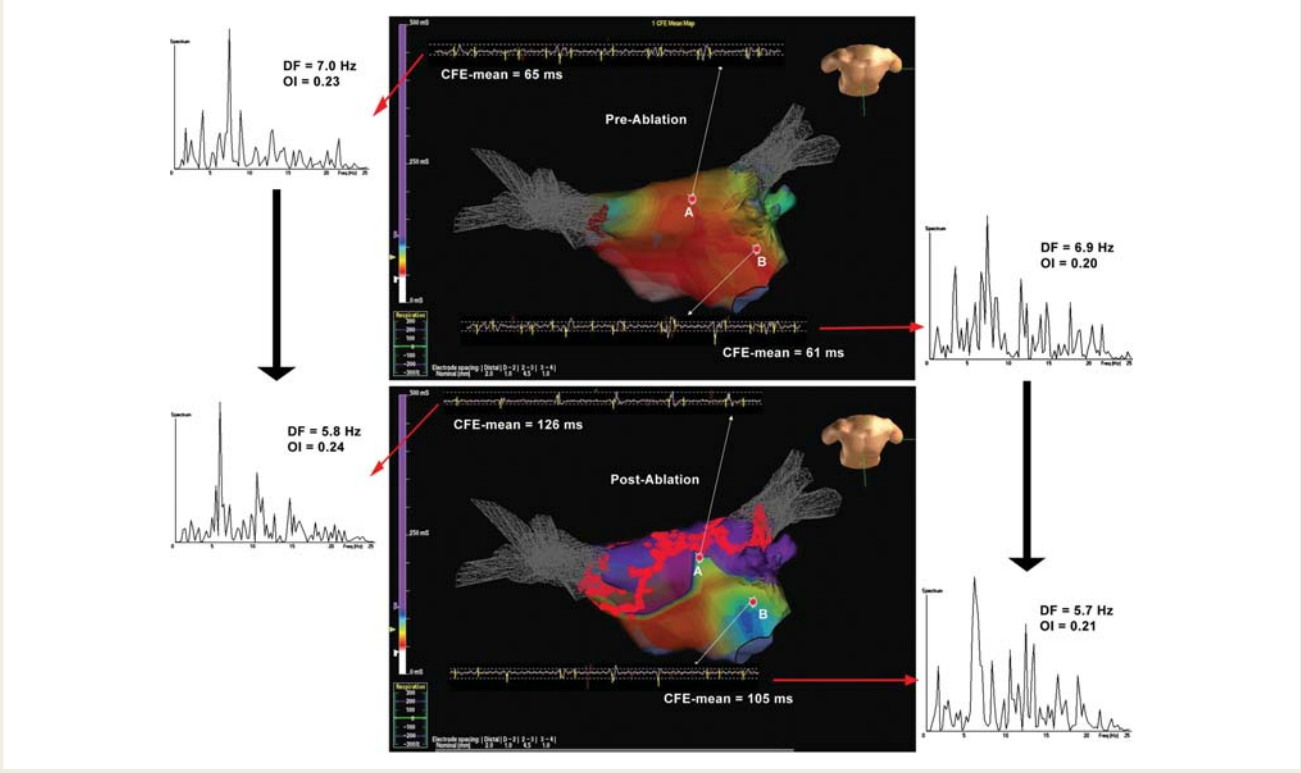

Figure 3 Example of the effect of ablation seen in a study patient. Pre- (top) and post-ablation (bottom) complex fractionated electrograms-mean maps are shown. The yellow markers on the electrograms indicate automatic detection of deflections meeting pre-specified complex fractionated electrograms-mean criteria as defined in *Figure 1*. Electrograms shown are 1 s representations of each regional recording lasting 8 s, with 4096 point Fast Fourier Transform shown adjacent to it. An increase in complex fractionated electrograms-mean and reduction in dominant frequency is observed at sites close to (point A) and distant from (point B) ablation lines.

in CFE-mean). Complex fractionated electrograms-mean increase was greater at sites close to ablation lines compared with sites distant from ablation lines, although corresponding DF decreased to a similar extent. Certain regions containing increasingly fractionated electrograms also seem to harbour high-frequency activation, suggesting that CFE and DF sites may be spatially related in some way. However, this relationship does not appear to be particularly strong, and ablation using an anatomical approach appears to affect these two parameters to different extents depending on proximity to the ablation lines, resulting in a weakening of their relationship following ablation. This could imply that though possibly related spatially, CFE and DF are probably not identical entities and could reflect either entirely different processes, or different components of the same substrate.

Complex fractionated electrograms

Konings *et al.*[11] previously described observation of different characteristics of unipolar electrograms during AF and it was

postulated that the different electrogram appearances represented specific patterns of conduction. Fragmented electrograms for example were shown to exist at areas with slow conduction or pivot points, which could represent sites of wavelet re-entry facilitating the maintenance of AF. Several studies have also verified using human subjects, that the distribution and location of CFE sites are usually stable and reproducible.[12,13] Nademanee *et al.*[4] took this concept further by targeting radiofrequency ablation at sites containing CFE within the atria, demonstrating high rates of AF termination with 91% of patients free of arrhythmia and symptoms at 1-year follow-up. However, subsequent studies by other authors using ablation targeted at CFE[14–16] have shown somewhat conflicting results, which in turn has cast doubt on our understanding of the significance of CFE.

Dominant frequency analysis

For many years, thoughts on the mechanism of AF was dominated by the multiple wavelet hypothesis put forward by Moe and Abildskov.[17] In recent years however, there has been more interest in the concept that AF may be more organized and focal, a theory which was previously proposed by Scherf *et al.*[18] Using experiments carried out on sheep hearts, Jalife and colleagues[19] demonstrated evidence of wave-front spatiotemporal periodicity during AF, with correlation between frequency of the periodic activity and global atrial DF. This, in conjunction with other supportive studies, have led to the proposal that relatively stable rotors giving rise to vortices of electrical waves could be responsible for maintaining AF.[20,21] Sanders *et al.*[5] carried out spectral analysis and frequency mapping of the atria in human AF and found that ablation at sites with high DF was associated with increased likelihood of terminating AF, hence highlighting the importance of high DF sites. By using a strategy of mapping and ablating maximal DF sites (in real-time) followed by circumferential pulmonary vein isolation, Atienza *et al.*[22] found that elimination of left atrial to right atrial frequency gradients was associated with long-term maintenance of sinus rhythm. A reduction in atrial DF measured from coronary sinus electrograms as well as from different sites within the LA can also be seen after circumferential pulmonary vein or electrogram-based ablation.[23] A critical decrease in DF by $\geq$11% has been proposed to be associated with maintenance of sinus rhythm after ablation of persistent AF.[24] It is therefore apparent that sites containing maximal DF could play a role in maintaining AF and that ablation to reduce local and global DF may confer long-term benefit.

Relevance of findings

Complex fractionated electrograms and DF appear to represent important substrates in the context of AF ablation but little is known with regard to whether they bear any relationship with each other or how they are affected by ablation. In our study, by using contact mapping at multiple sites within the left atrium, we have demonstrated the characteristics of regional and global CFE and DF pre- and post-ablation using an anatomically guided technique of wide area circumferential ablation around the pulmonary veins together with left atrial roof ablation. Degree of fractionation (inversely related to CFE-mean) and DF reduced following ablation targeted at isolation of the pulmonary veins, which is in agreement with recently published work by Lin *et al.*[25] This trend is consistent at a local as well as a global atrial level, even at sites distant from ablation lines, suggesting dynamic interaction between pulmonary veins and atrium in persistent AF. Our findings also suggest a possible spatial link between CFE-mean and DF of atrial electrograms, although direct correlation is not strong. In a significant number of cases, the highest DF sites were found adjacent to sites with the lowest CFE-mean, rather than at the same site. This is in keeping with results from animal studies carried out by Kalifa *et al.*[26] where the greatest fractionation in sheep AF was seen at the peripheries or outer boundaries of maximal DF sites. This is an observation which was also reported by Stiles *et al.*[27] who carried out high density mapping on a subset of 10 patients with persistent AF. Using activation mapping, the authors found that CFE sites were usually located adjacent to sites with high DF. Complex fractionated electrograms and DF correlation was observed in their study but this was restricted to within an individual but not point-by-point basis. Using a larger group of patients in persistent AF, our study has gone further to show that regional CFE-mean and DF appear to be affected to different degrees by ablation, adding support to the notion that the relationship between fractionation and DF is probably not a direct one.

Previous studies have suggested increased likelihood of the presence of CFE at atrial sites innervated by ganglionated plexi.[28,29] These autonomic tissues are typically located in the antral regions around pulmonary veins and are usually within the path of ablation lesions delivered using standard circumferential pulmonary vein isolation techniques. This could explain the greater change in CFE-mean compared with change in DF seen in our study, as the ablation strategy used would have encompassed locations of ganglionated plexi.

Although the study was not powered for assessing the influence of amiodarone, the results appear to indicate that pre-treatment with amiodarone may result in a lower degree of AF electrogram fractionation and reduced DF, as well as increased organization while the effects of ablation on DF and fractionation are preserved. Further studies are required to better understand the effects of amiodarone on the spectral characteristics of AF and their interaction with ablation.

The overall implications from our study are that although CFE-mean and DF are not identical spatial entities, they seem to occur in close proximity to each other, and respond to different extents with ablation. Head-to-head studies comparing ablation of each substrate or both are needed to determine if they result in any differences in outcomes. In our study, although ablation resulted in desired changes in both CFE-mean and DF, the relative change is greater in the former near sites of ablation lines. This suggests that CFE may represent a more local phenomenon than DF and its change more reflective of the degree of substrate modification near the site of ablation. One practical implication from our study could be that an approach delivering linear ablation lesions should probably incorporate locations with high degree of fractionation first (as opposed to DF). Further studies are required to test these hypotheses and the effects of different approaches to ablation targets.

Limitations

Our study involved a relatively small sample of patients and we used sequential contact mapping of the atrium. Higher density simultaneous atrial mapping could provide more detailed information but this would be technically more challenging. Mapping of the right atrium was also not carried out in our study. It has however, been shown by other studies that the LA plays a greater role in driving AF as it usually contains sites with higher frequency of activation in persistent AF.[27,30]

Conclusion

The role of substrate modification in ablation of persistent AF needs to be more clearly defined and our study has provided further insight into the characteristics of electrogram fractionation and DF in persistent AF before and after limited left atrial ablation. Our findings suggest that CFE and DF exhibit a degree of spatial relationship, although not a close one, and are also affected to different extents by ablation, suggesting that they may either be entirely separate entities or reflect different components of the same substrate. Further studies comparing the long-term outcomes of CFE and DF targeted ablation or a combined ablation strategy of both substrates are needed to help clarify their clinical significance and relevance.

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References

1. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ *et al.* Hrs/ehra/ecas expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the heart rhythm society (hrs) task force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2007;**4**:816–61.
2. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G *et al.* Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation* 2004;**109**:327–34.
3. Po SS, Nakagawa H, Jackman WM. Localization of left atrial ganglionated plexi in patients with atrial fibrillation. *J cardiovas electrophysiol* 2009;**20**:1186–9.
4. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T *et al.* A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;**43**:2044–53.
5. Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, Hsu LF *et al.* Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. *Circulation* 2005;**112**:789–97.
6. Stiles MK, Brooks AG, John B, Wilson L, Kuklik P, Dimitri H *et al.* The effect of electrogram duration on quantification of complex fractionated atrial electrograms and dominant frequency. *J Cardiovasc Electrophysiol* 2008;**19**:252–8.
7. Lin YJ, Tai CT, Kao T, Chang SL, Wongcharoen W, Lo LW *et al.* Consistency of complex fractionated atrial electrograms during atrial fibrillation. *Heart Rhythm* 2008;**5**:406–12.
8. Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M *et al.* Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the langendorff-perfused sheep heart. *J Cardiovasc Electrophysiol* 2000;**11**:869–79.
9. Tuan J, Osman F, Jeilan M, Kundu S, Mantravadi R, Stafford PJ *et al.* Increase in organization index predicts atrial fibrillation termination with flecainide post-ablation: spectral analysis of intracardiac electrograms. *Europace* 2010;**12**:488–93.
10. Takahashi Y, Sanders P, Jais P, Hocini M, Dubois R, Rotter M *et al.* Organization of frequency spectra of atrial fibrillation: relevance to radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2006;**17**:382–8.
11. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation* 1997;**95**:1231–41.
12. Verma A, Wulffhart Z, Beardsall M, Whaley B, Hill C, Khaykin Y. Spatial and temporal stability of complex fractionated electrograms in patients with persistent atrial fibrillation over longer time periods: relationship to local electrogram cycle length. *Heart Rhythm* 2008;**5**:1127–33.
13. Roux JF, Gojraty S, Bala R, Liu CF, Hutchinson MD, Dixit S *et al.* Complex fractionated electrogram distribution and temporal stability in patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2008;**19**:815–20.
14. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z *et al.* A prospective, multicenter evaluation of ablating complex fractionated electrograms (cfes) during atrial fibrillation (af) identified by an automated mapping algorithm: acute effects on af and efficacy as an adjuvant strategy. *Heart Rhythm* 2008;**5**:198–205.
15. Oral H, Chugh A, Good E, Wimmer A, Dey S, Gadeela N *et al.* Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. *Circulation* 2007;**115**:2606–12.
16. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T *et al.* A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. *J Am Coll Cardiol* 2009;**53**:782–9.
17. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart Jl* 1959;**58**:59–70.
18. Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J* 1948;**36**:241–51.
19. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation* 1998;**98**:1236–48.
20. Jalife J, Berenfeld O, Skanes A, Mandapati R. Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? *J Cardiovasc Electrophysiol* 1998;**9**:S2–12.
21. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* 2002;**54**:204–16.
22. Atienza F, Almendral J, Jalife J, Zlochiver S, Ploutz-Snyder R, Torrecilla EG *et al.* Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. *Heart Rhythm* 2009;**6**:33–40.
23. Lemola K, Ting M, Gupta P, Anker JN, Chugh A, Good E *et al.* Effects of two different catheter ablation techniques on spectral characteristics of atrial fibrillation. *J Am Coll Cardiol* 2006;**48**:340–8.
24. Yoshida K, Chugh A, Good E, Crawford T, Myles J, Veerareddy S *et al.* A critical decrease in dominant frequency and clinical outcome after catheter ablation of persistent atrial fibrillation. *Heart Rhythm* 2010;**7**:295–302.
25. Lin YJ, Tai CT, Kao T, Chang SL, Lo LW, Tuan TC *et al.* Spatiotemporal organization of the left atrial substrate after circumferential pulmonary vein isolation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2009;**2**:233–41.
26. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D *et al.* Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation* 2006;**113**:626–33.
27. Stiles MK, Brooks AG, Kuklik P, John B, Dimitri H, Lau DH *et al.* High-density mapping of atrial fibrillation in humans: relationship between high-frequency activation and electrogram fractionation. *J Cardiovasc Electrophysiol* 2008;**19**:1245–53.
28. Lemery R, Birnie D, Tang ASL, Green M, Gollob M. Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. *Heart Rhythm* 2006;**3**:387–96.
29. Katritsis D, Giazitzoglou E, Sougiannis D, Voridis E, Po SS. Complex fractionated atrial electrograms at anatomic sites of ganglionated plexi in atrial fibrillation. *Europace* 2009;**11**:308–15.
30. Wu TJ, Doshi RN, Huang HL, Blanche C, Kass RM, Trento A *et al.* Simultaneous biatrial computerized mapping during permanent atrial fibrillation in patients with organic heart disease. *J Cardiovasc Electrophysiol* 2002;**13**:571–7.