Organization of Frequency Spectra of Atrial Fibrillation: Relevance to Radiofrequency Catheter Ablation

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Organization of Frequency Spectra of Atrial Fibrillation: Relevance to Radiofrequency Catheter Ablation. ***Introduction:*** **We hypothesized that the frequency spectra of fibrillatory electrograms may reflect the complexity of activities perpetuating atrial fibrillation (AF). To test this hypothesis, we evaluated the frequency spectra in patients with paroxysmal AF in relation to catheter ablation.**

Methods and Results: **This study comprised two protocols: 25 patients undergoing pulmonary vein (PV) isolation in protocol I, and 20 patients undergoing mitral isthmus linear ablation after PV isolation in protocol II. The mean of dominant frequency (DF) and organization index (the ratio of the area under the DF and its harmonics to the total power) were determined from 32-second recordings in the coronary sinus. In protocol I, a PV was considered "driver" of AF if isolation of the PV resulted in termination or slowing of AF (decrease in DF by $\geq$0.25 Hz). Twenty-one patients had AF termination during four PV isolation. Among these 21 patients, 13 patients with single driving PV showed significantly higher baseline organization index than eight patients with multiple driving PVs (0.45 $\pm$ 0.08 vs 0.35 $\pm$ 0.07, P $=$ 0.009). Patients with multiple driving PVs showed a significant increase in the organization index to 0.45 $\pm$ 0.11 (P $<$ 0.05) after isolation of the initial driving PVs. In protocol II, the baseline organization index was significantly higher in seven patients who had termination of AF during mitral isthmus ablation than 13 patients who did not (0.50 $\pm$ 0.10 vs 0.38 $\pm$ 0.07, P $<$ 0.008). The baseline DF was not associated with outcomes of ablation in both protocols.**

Conclusions: **A higher organization index of atrial electrograms is associated with termination of AF during limited ablation. This parameter may be useful to anticipate the extent of ablation.** *(J Cardiovasc Electrophysiol, Vol. 17, pp. 382-388, April 2006)*

fibrillation, ablation, frequency, organization, pulmonary vein, mitral isthmus

Introduction

Although the mechanism of atrial fibrillation (AF) remains controversial, successful treatment of AF by nonpharmacological therapy has provided insights into its mechanism. The observation of prolongation of the AF cycle length (AFCL) and termination of AF during pulmonary vein (PV) isolation has implicated the PV as a driving source of activity maintaining paroxysmal AF.[1] On the other hand, the potential role of macro-reentrant circuits is supported by the efficacy of surgical maze procedure and catheter-based linear ablation.[2–4] Recently, spectral analysis which has been used for analysis of complex electrograms during AF in order to reveal hidden organization[5,6] demonstrated the presence of driving sources using a 3D navigation system.[7]

We hypothesized that spectral analysis of atrial electrograms may characterize the ongoing fibrillatory process, thus being helpful for identifying forms of AF amenable to limited catheter ablation. In protocol I, PV isolation was performed during persistent AF to evaluate the number of PVs contributing to the fibrillatory process (driving PV), and the baseline frequency spectra were characterized by the number of the driving PVs. In protocol II, mitral isthmus linear ablation was performed during persistent AF after PV isolation to evaluate the baseline characteristics of the frequency spectra in patients who had termination of AF during this procedure.

Methods

Study Population

Protocol I comprised 25 patients with paroxysmal AF who underwent isolation of all PVs, and protocol II comprised 20 patients with paroxysmal AF who underwent mitral isthmus linear ablation after PV isolation. These protocols were performed during two different inclusion periods. All patients had undergone cavotricuspid isthmus ablation, but no previous left atrial linear ablation. Patients were selected on the basis of having induced or spontaneously persistent AF of a minimal duration of 10 minutes. Ten of 25 patients (40%) were in spontaneous AF at the commencement of PV isolation in protocol I, and 12 of 20 patients (60%) were in spontaneous AF at the commencement of mitral isthmus ablation in protocol II. Anti-arrhythmic drugs except amiodarone were discontinued $\geq$5 half-lives prior to ablation, and amiodarone

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TABLE 1

Baseline Characteristics of Patients

	Protocol I (n = 25)	Protocol II (n = 20)	P Value
Age (years)	55 ± 9	52 ± 11	0.3
Female	2 (8%)	2 (10%)	>0.99
Structural heart disease	2 (8%)	0 (0%)	0.5
Hypertension	3 (12%)	2 (10%)	>0.99
AF duration (months)	85 ± 55	104 ± 60	0.3
Maximal duration of a episode (hours)	49 ± 43	89 ± 94	0.09
Left ventricular ejection fraction (%)	66 ± 12	65 ± 9	0.6
Parasternal LA diameter (mm)	43 ± 5	42 ± 5	0.3
Longitudinal LA diameter (mm)	54 ± 11	56 ± 6	0.5
Transverse LA diameter (mm)	38 ± 8	41 ± 7	0.4

was discontinued three months prior to ablation. Baseline characteristics of patients are presented in Table 1. In both protocols, there was no significant difference in baseline characteristics between patients in spontaneous AF and those in induced AF. All patients gave written informed consent.

Electrophysiological Study

All patients had effective anticoagulation for >1 month and transesophageal echocardiography to exclude thrombus in the left atrium before ablation.

For the ablation procedure, a 6Fr quadripolar catheter (Xtrem, Ela Medical, Montrouge, France) was positioned in the coronary sinus (CS). A 10-pole circumferential catheter (Lasso, Biosense-Webster, Diamond Bar, CA) for PV ostial mapping and a 4-mm irrigated-tip ablation catheter (Biosense-Webster) were utilized. Surface electrocardiogram and intracardiac electrograms were measured at a paper speed of 100 mm/sec utilizing a digital amplifier/recording system (Bard Electrophysiology, Lowell, MA). A single bolus of 50 IU/kg of heparin was administered after the transseptal puncture and repeated only for procedures lasting more than four hours.

Signal Processing and Frequency Domain Analysis

Frequency domain analysis was performed for one bipolar electrogram positioned in the ostium∼proximal CS at the stable location to allow serial measurement. We selected the bipolar recording showing no or minimal ventricular potentials (<10% of atrial signal amplitude). At first, intracardiac electrograms were recorded with a filtering from 30 to 500 Hz, which was identical to the one commonly used in electrophysiological study. Thereafter, the absolute value of the filtered signal was low-pass filtered at 20 Hz. This filtering process extracts high-frequency components, and transforms a complex waveform into a series of atrial activations that underline the possible periodicity of the signal by reduction of the effects of varying electrogram morphology or amplitude.[8-10]

After signal processing, a fast Fourier transform (FFT) was performed over a sliding four-second window of 4,096 points every one second from 32-second recordings. Thus, 28 consecutive windows were analyzed in each recording. The largest peak in the resulted magnitude spectrum was defined as a dominant frequency (DF). To measure the periodicity of the signal and the variability of frequency in the spectrum, the power of the DF and its harmonics was estimated by computing the area under the DF and its harmonics. The ratio of this area to the total power was defined as the organization index. Higher organization index is considered to represent less variability of frequency in the CS in a four-second window (Fig. 1). The mean DF and organization index from all 28 windows were determined. Signal processing and FFT computation were performed by a dedicated system (Bard Electrophysiology).

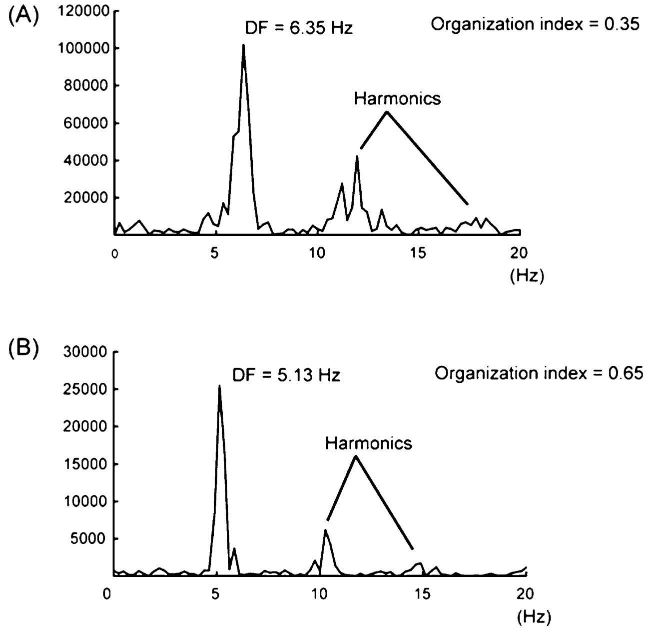

Figure 1. *Frequency spectra from a four-second window. The frequency with the largest peak (dominant frequency: DF) was 6.35 Hz in A and 5.13 Hz in B. Harmonics of the DF were seen in each. A: Note the broad peaks in frequency spectra with low organization index. B: Note the narrow peaks in DF and its harmonics with the higher organization index.*

Protocol I: Pulmonary Vein Isolation

Temporal stability of frequency spectra

First, the mean DF and organization index were measured repeatedly with an interval >5 minutes prior to catheter ablation for evaluation of their temporal stability.

Correlation between frequency spectra and cycle length

To examine whether the frequency spectra represent local activity, the mean of AFCL and its standard deviation from all cycles from the bipolar electrograms in the same period were determined and correlated with DF and organization index, respectively. Cycle length measurement was performed by a dedicated system (Bard Electrophysiology), and the detection of potentials was manually checked. Interelectrogram intervals of <50 ms and continuous activity were counted as a single activity.

Catheter ablation

PV isolation was commenced during persistent AF to evaluate the effect of these procedures on the maintenance of AF. For PV isolation, radiofrequency (RF) application was delivered at 1 cm proximal to the posterior ostium of all PVs and the anterior ostium of right PVs with a power limit of 30 W.[11] At the anterior ostium of left PVs and the inferior ostium of both inferior PVs, RF was applied at the rim of PV ostium with a power limit of 25 W. If ipsilateral PVs were located closely or common ostium was observed, RF lesions for each PV were connected and these two PVs were isolated en bloc. Ablation catheter was dragged every 30–60 seconds with continuous RF delivery. The endpoint of PV isolation was circumferential elimination or dissociation of PV potential.

Effects of driving PV on frequency spectra

The mean DF and organization index were determined prior to ablation and after disconnection of each PV. A PV was considered as a *driving PV* if disconnection of the PV results in (1) termination of AF or (2) a decrease in DF by ≥0.25 Hz (corresponding to ≈ a 10 ms increase in cycle length for a DF of 5.0 Hz). Termination of AF was defined as conversion into atrial flutter or sinus rhythm. AF was defined as rapid atrial rhythm with a characteristic surface electrogram morphology and beat-to-beat cycle length variability >30 ms, morphology, and/or amplitude of recorded bipolar electrograms.[12] Atrial flutter was defined as a rapid atrial rhythm with a regular and monomorphic ECG pattern, and variability of cycle length ≤30 ms. Disconnection of PVs was performed in a randomized order to assess whether specific PVs were more likely to have an impact on fibrillatory process.

Protocol II: Mitral Isthmus Linear Ablation

The mean DF and organization index were determined prior to mitral isthmus ablation (after disconnection of all PVs). Mitral isthmus ablation was performed during persistent AF to assess the impact of this linear lesion to the fibrillatory process. The baseline DF and organization index were compared between patients in whom AF terminated and those in whom AF did not terminate during mitral isthmus ablation.

Catheter ablation

A delivered power was 30–38 W and a temperature setting was 50°C for RF delivery from the endocardium.[3] Ablation was begun from the mitral annulus, where both atrial potentials and ventricular potentials were recorded with the ratio of potential amplitude 1:1 to 2:1. RF was delivered for 30–60 seconds at the same site, and the ablation catheter was dragged to a contiguous site in the direction of the left inferior PV after >50% of reduction or splitting of the local atrial potentials. After endocardial ablation, RF was optionally applied in the CS to target epicardial gap using a delivered power of 25 W and a temperature setting of 50°C. If AF persisted despite abolition of local atrial potentials after ablation at the endocardium and within the CS, electrical cardioversion was performed to validate conduction block. Conduction block was demonstrated by a corridor of double potentials, an activation detour, and/or differential pacing techniques during pacing adjacent to the line.[3]

Statistical Analysis

Continuous variables are presented as mean ± SD or proportions. The data distributed normally was analyzed by Student's *t*-test, and the data not distributed normally was analyzed by Mann-Whitney *U* test or Wilcoxon signed rank test. Correlation coefficients were calculated by the Pearson method. Categorical variables are presented as number and percentage, and compared by Fisher's exact test. A two-sided $P < 0.05$ was considered statistically significant.

Results

Protocol I

Temporal stability of frequency domain analysis

The mean of DF and organization index prior to PV isolation were 5.77 ± 0.73 Hz and 0.41 ± 0.09, respectively. The difference between the first and second measurements of mean DF and organization index were 0.01 ± 0.16 Hz ($P = 0.88$) and 0.01 ± 0.08 ($P = 0.64$), respectively, indicating temporal stability of these parameters.

Correlation between frequency spectra and cycle length

The inverse frequency of mean DF (1,000/DF in ms) showed a strong positive linear correlation with mean AFCL (evaluated from 221 ± 29 cycles) measured during the same period ($P < 0.0001$, $r = 0.945$; Fig. 2A). Mean organization index and standard deviation of AFCL also showed a linear correlation ($P < 0.0001$, $r = -0.451$; Fig. 2B).

Pulmonary vein isolation

During PV isolation, AF terminated in 21 patients (84%; Fig. 3A): during isolation of the first targeted PV in five patients (20%), second targeted PV in seven patients (28%), third targeted PV in seven patients (28%), and fourth targeted PV in two patients (8%). The targeted PV where AF terminated during ablation is shown in Table 2.

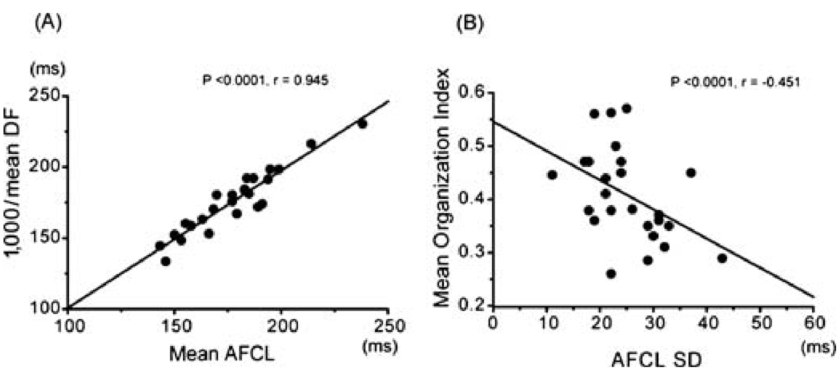

Figure 2. *A: Relationship between the inverse frequency of mean dominant frequency (DF) (1,000/mean DF in ms) and the mean atrial fibrillatory cycle length (AFCL) measured during the same period ($P < 0.0001$, $r = 0.945$). B: Relationship between the mean organization index and the standard deviation of AFCL ($P < 0.0001$, $r = -0.451$).*

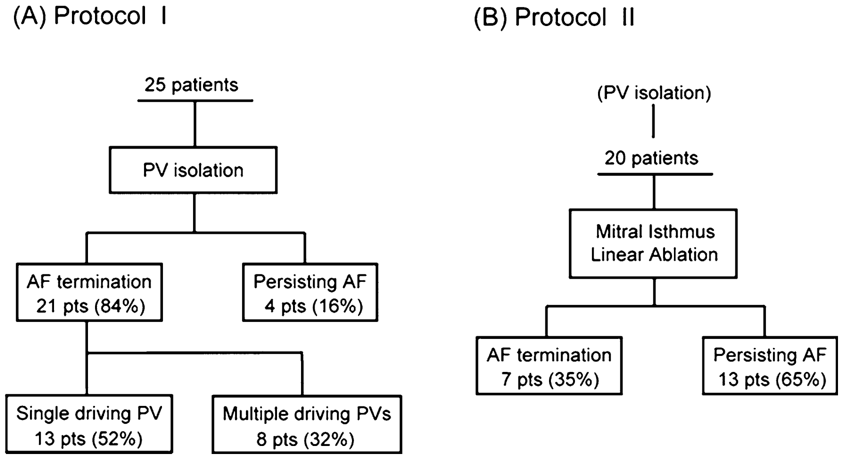

Figure 3. *A: Protocol I: Termination of atrial fibrillation (AF) during pulmonary vein (PV) isolation and the number of driving PVs in these patients. B: Protocol II: Termination of AF during mitral isthmus linear ablation.*

A total of 96 PVs in 25 patients were isolated (4 PVs had common ostia) by 37 ± 11 minutes of RF energy delivery and 65 ± 17 minutes of the procedural duration. Thirty-seven of 96 PVs (39%) were identified as driving PVs: isolation of 21 PVs (22%) resulted in termination of AF, and isolation of 16 PVs (17%) resulted in a decrease in DF by ≥0.25 Hz (mean decrease: 0.55 ± 0.31 Hz). Single driving PV was identified in 14 patients (56%), two driving PVs in nine patients (36%), and three driving PVs in two patients (8%). No patient had four driving PVs. The location of these driving PVs was a similar incidence among each of four PVs, but all PVs with common ostium were driving PVs (Table 2).

Among 21 patients who had termination of AF, 13 patients had a single driving PV and eight patients had multiple driving PVs (two driving PVs in six patients and three driving PVs in two patients; Fig. 3A). The baseline organization index was significantly higher in patients who had a single driving PV than those who had multiple driving PVs (0.45 ± 0.08 [range: 0.31–0.57] vs 0.35 ± 0.07 [range: 0.26–0.45], $P = 0.009$), although there was no difference in the baseline DF (5.45 ± 0.59 Hz [range: 4.34–6.30 Hz] vs 5.80 ± 0.64 Hz [range: 5.04–6.92 Hz], $P = 0.31$). In addition, in eight patients with multiple driving PVs, the organization index was compared between baseline and after isolation of the initial one or two driving PVs: i.e., before ablation of the last driving PV. Isolation of the initial driving PVs resulted in a significant increase in the organization index from 0.35 ± 0.07 (range: 0.26–0.45) to 0.45 ± 0.11 (range: 0.31–0.67, $P < 0.05$).

TABLE 2

The Targeted Pulmonary Vein (PV) Where Atrial Fibrillation (AF) Terminated During Ablation and the Incidence of Driving PV

	AF Termination	Driving PV
LSPV	7 pts (28%)	9/23 (39%) PVs
LIPV	5 pts (20%)	6/23 (26%) PVs
RSPV	3 pts (12%)	7/23 (30%) PVs
RIPV	4 pts (16%)	11/23 (48%) PVs
Left common PV	1 pt (4%)	2/2 (100%) PVs
Right common PV	1 pt (4%)	2/2 (100%) PVs

Two patients had the common ostium of left PVs and two patients had the common ostium of right PVs. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

Protocol II

Mitral isthmus ablation

During mitral isthmus ablation, AF persisted in 13 patients (65%) and AF terminated in seven patients (35%; Fig. 3B); AF converted directly to sinus rhythm in five patients, by conversion into left atrial roof dependent atrial flutter in one and peri-mitral atrial flutter in one. RF duration delivered during AF was similar between patients with and without termination of AF (7.0 ± 6.3 minutes [range: 2.0–20.1] vs 11.4 ± 6.9 minutes [range: 3.0–28.0], $P = 0.15$).

The baseline DF was not significantly different between patients with AF termination and those with persistent AF (5.29 ± 0.74 [range: 4.46–6.23] Hz vs 5.72 ± 0.73 [range: 4.71–6.88] Hz, $P = 0.17$; Fig. 4). In contrast, the baseline organization index was significantly higher in patients with AF termination than those with persistent AF (0.50 ± 0.10 [range: 0.38–0.63] vs 0.38 ± 0.07 [range: 0.28–0.49], $P < 0.008$; Fig. 4).

Discussion

The present study demonstrates the following results: (1) termination of AF by ablation of a single target (single PV or single linear lesion) was associated with an initial higher organization index of atrial electrograms; (2) in patients with multiple driving PVs, the organization index increases by isolation of driving PVs prior to termination of AF. These results suggest that the organization index is helpful for identifying forms of AF amenable to limited ablation.

Organization Index and Number of Driving Pulmonary Veins

Epicardial mapping of ongoing AF demonstrated activities originating from the PV or its ostium, suggesting its driving role of AF.[13] Moreover, it was demonstrated that isolation of the PV initially increases AFCL, culminating in termination of AF.[1] In the present study, a decrease in the DF or termination of AF was observed at the time of disconnection of 39% of PVs. This is consistent with the previous reports and indicates that activities from these PVs contributed to the frequency spectra of atrial electrograms. When multiple driving PVs were present, the activities from these PVs may have resulted in multiple components in the frequency spectra (lower organization index), i.e., more chaotic electrograms

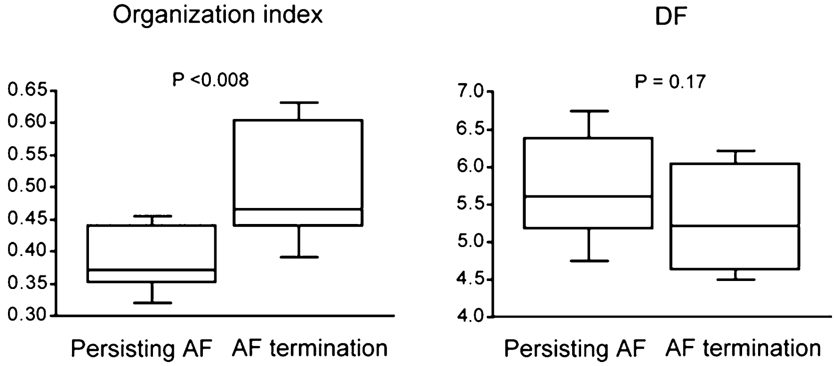

Figure 4. *Comparison of the baseline organization index and dominant frequency between patients with atrial fibrillation (AF) termination and persistent AF during mitral isthmus linear ablation.*

(Fig. 5). This was confirmed by isolation of the initial driving PV, which increased the organization index from 0.35 to 0.45, reaching a value similar to the baseline organization index in patients with a single driving PV. Therefore, the presence of multiple driving sources is one important cause of multiple peaks in the frequency spectra. Interestingly, the incidence of driving PVs was similar among all four PVs in the present study, while triggering ectopic beats and dissociated activity have more frequently been described in the superior PVs.[14-17]

Termination of AF During Mitral Isthmus Linear Ablation

Termination of AF by mitral isthmus linear lesion was observed in patients with high organization index. This also indicates that limited ablation (single PV isolation or single linear lesion) is effective in terminating AF in patients with high organization index. However, the present study cannot identify the characteristics in the frequency spectra predictive of the appropriate location for ablation lesions.

While the mechanism of termination of AF during PV isolation is linked to activities originating from the PV or its ostium due to focal discharge or reentry in the PV,[13,14,18,19] the mechanism of termination of AF during mitral isthmus linear ablation is not known. This may include: (1) interruption of wavelets or macro-reentrant circuit propagating through the mitral isthmus or (2) elimination of focal sources located in the trajectory of the linear lesion (e.g., ligament of Marshall[20]).

Previous Studies

It has been demonstrated that in the presence of mother rotor, the variability of frequency (the organization index) is increased at the site remote from the driver due to fibrillatory conduction.[21] Everett et al. showed that higher organization

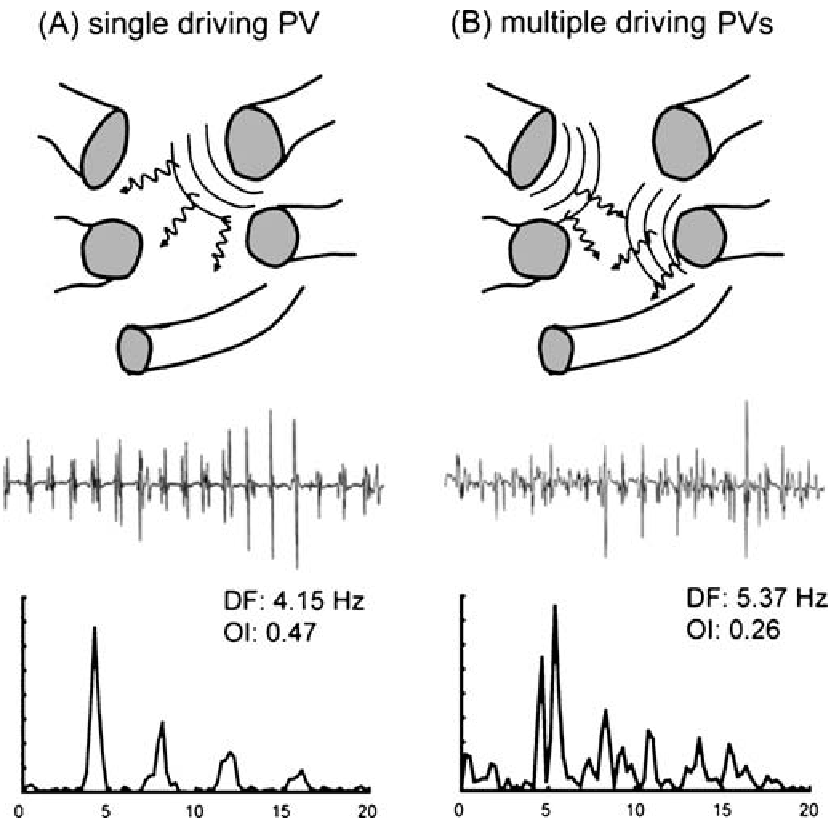

Figure 5. ***Top:*** *Schema of fibrillatory process in patients with single driving pulmonary vein (PV) (A) and multiple driving PVs (B).* ***Middle:*** *Examples of four-second recordings in the coronary sinus in each.* ***Bottom:*** *Frequency spectra from the recording in the middle panel. Note that multiple frequency components and the low organization index (B, bottom panel) are observed in a case of multiple driving PVs.*

index was associated with lower atrial defibrillation threshold in animal models,[9] leading to the hypothesis that a higher organization index is associated with increased organization of AF or smaller number of wavelets. In addition, the present study indicates that the number of driving sources is also a factor associated with the organization index.

Clinical Implications

Frequency domain analysis may be useful for following the effects of ablation on the fibrillatory process during the procedure. Mean DF from 32-second recordings was strongly correlated with mean AFCL, which has been proposed as a parameter for monitoring substrate changes during catheter ablation of ongoing AF.[1]

The organization index may be used as an additional parameter during catheter ablation in order to suggest the extent of ablation required for termination of AF. A high organization index was associated with the presence of limited activity driving the atria. If multiple sources are driving the atria, activities from each source collide and interact with each other, producing a broad band with multiple peaks in the frequency spectra (low organization index). Frequency mapping with use of a 3D navigation system has been able to identify the location of driving sources[7]; however, this method requires additional procedural duration. The simple technique used in the present study is applicable to conventional procedure.

Limitations

The main limitation of this study is that recording from a single site was used for frequency domain analysis to evaluate global fibrillatory process. In previous studies, however, AFCL from a single site was demonstrated to be related to AF duration or substrate modification by ablation.[1,22,23] The CS is the optimal measurement site to allow repeated serial measurements during the procedure because of stability of the catheter. For PV isolation, ablation lesions were deployed remote from the CS, thus resulting in minimal effects on local electrophysiological properties around the CS. On the other hand, mitral isthmus ablation may directly influence electrograms in the CS, but frequency domain analysis was not performed after this ablation.

We assessed mean DF and organization index of 28 consecutive windows from 32-second recordings, which were demonstrated to be temporally stable. Temporal stability of fibrillatory wave frequency was reported with the use of surface ECG over 24 hours.[24] However, spontaneous changes in fibrillatory process (generation or extinction of driving sources, etc.) may have influenced results of frequency domain analysis. It is likely that the contribution of short-lived bursts of activity may not have been recognized in such an analysis.

If multiple PVs were driving the atria, a decrease in DF caused by isolation of a given PV is evidence for a contributing role of this PV (“driving PV”), while no change in DF allows no conclusion on the involvement of the isolated PV in fibrillatory process. This study possibly underestimates the number of “driving PVs.”

Finally, these results have been observed in a select group of patients with paroxysmal AF; whether these findings can be extrapolated to patients with persistent or permanent AF was not evaluated in this study.

Conclusion

A higher organization index of atrial electrograms is associated with termination of AF during limited ablation; and organization index increases by elimination of driving PVs. This simple method may characterize the complexity of the fibrillatory process and be useful to anticipate the extent of ablation and monitor the effects of ablation during the procedure.

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References

1. Haissaguerre M, Sanders P, Hocini M, Hsu LF, Shah DC, Scavee C, Takahashi Y, Rotter M, Pasquie JL, Garrigue S, Clementy J, Jais P: Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. Circulation 2004;109:3007-3013.
2. Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG: Five-year experience with the maze procedure for atrial fibrillation. Ann Thorac Surg 1993;56:814-823.
3. Jais P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clementy J, Haissaguerre M: Technique and results of linear ablation at the mitral isthmus. Circulation 2004;110:2996-3002.
4. Gaita F, Riccardi R, Caponi D, Shah D, Garberoglio L, Vivalda L, Dulio A, Chiecchio A, Manasse E, Gallotti R: Linear cryoablation of the left atrium versus pulmonary vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease: Correlation of electroanatomic mapping and long-term clinical results. Circulation 2005;111:136-142.
5. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J: Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. Circulation 1998;98:1236-1248.
6. Berenfeld O, Mandapati R, Dixit S, Skanes AC, Chen J, Mansour M, Jalife J: Spatially distributed dominant excitation frequencies reveal hidden organization in atrial fibrillation in the Langendorff-perfused sheep heart. J Cardiovasc Electrophysiol 2000;11:869-879.
7. Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, Hsu LF, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavee C, Ploutz-Snyder R, Jalife J, Haissaguerre M: Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005;112:789-797.
8. Botteron GW, Smith JM: Quantitative assessment of the spatial organization of atrial fibrillation in the intact human heart. Circulation 1996;93:513-518.
9. Everett TH, Moorman JR, Kok LC, Akar JG, Haines DE: Assessment of global atrial fibrillation organization to optimize timing of atrial defibrillation. Circulation 2001;103:2857-2861.
10. Lazar S, Dixit S, Marchlinski FE, Callans DJ, Gerstenfeld EP: Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. Circulation 2004;110:3181-3186.
11. Hocini M, Sanders P, Jais P, Hsu LF, Takahashi Y, Rotter M, Clementy J, Haissaguerre M: Techniques for curative treatment of atrial fibrillation. J Cardiovasc Electrophysiol 2004;15:1467-1471.
12. Wells JL Jr, Karp RB, Kouchoukos NT, MacLean WA, James TN, Waldo AL: Characterization of atrial fibrillation in man: Studies following open heart surgery. Pacing Clin Electrophysiol 1978;1:426-438.
13. Wu TJ, Doshi RN, Huang HLA, Blanche C, Kass RM, Trento A, Cheng W, Karagueuzian HS, Peter CT, Chen PS: Simultaneous biatrial computerized mapping during permanent atrial fibrillation in patients with organic heart disease. J Cardiovasc Electrophysiol 2002;13:571-577.
14. Takahashi Y, Iesaka Y, Takahashi A, Goya M, Kobayashi K, Fujiwara H, Hiraoka M: Reentrant tachycardia in pulmonary veins of patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2003;14:927-932.
15. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J: Spontaneous

initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666.
16. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, Hsu TL, Ding YA, Chang MS: Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999;100:1879-1886.
17. Weerasooriya R, Jais P, Scavee C, Macle L, Shah DC, Arentz T, Salerno JA, Raybaud F, Choi KJ, Hocini M, Clementy J, Haissaguerre M: Dissociated pulmonary vein arrhythmia: Incidence and characteristics. J Cardiovasc Electrophysiol 2003;14:1173-1179.
18. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, Vaz D, Olgin JE: Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. Circulation 2003;107:1816-1821.
19. Chou CC, Nihei M, Zhou S, Tan A, Kawase A, Macias ES, Fishbein MC, Lin SF, Chen PS: Intracellular calcium dynamics and anisotropic reentry in isolated canine pulmonary veins and left atrium. Circulation 2005;31:31.
20. Hwang C, Wu TJ, Doshi RN, Peter CT, Chen PS: Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. Circulation 2000;101:1503-1505.
21. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J: Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. Circulation 2001;103:2631-2636.
22. Wijffels MCEF, Kirshhof CJHJ, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. Circulation 1995;92:1954-1968.
23. Sih HJ, Berbari EJ, Zipes DP: Epicardial maps of atrial fibrillation after linear ablation lesions. J Cardiovasc Electrophysiol 1997;8:1046-1054.
24. Xi Q, Sahakian AV, NG J, Swiryn S: Atrial fibrillatory wave characteristics on surface electrogram: ECG to ECG repeatability over twenty-four hours in clinically stable patients. J Cardiovasc Electrophysiol 2004;15:911-917.