

Differences of BiAtrial Substrate Properties in Patients with Different Types of AF

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and induces cardiac dysfunction and strokes. The development of AF requires a “trigger” and also an electroanatomic “substrate” capable of both initiating and perpetuating AF. Over the past decade, the understanding of the AF substrate properties in both atria has increased with fractionation and frequency analyses of the local atrial electrograms using three-dimensional electroanatomic mapping systems. The purpose of this review was to discuss the differences in the atrial substrate properties in patients with different types of AF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and induces cardiac dysfunction and strokes.^{1,2} It is well known that AF depends on the interaction between the triggers and substrate.^{3,4} The elimination or isolation of the pulmonary vein (PV) and non-PV triggers has been the basis of most AF ablation strategies and has been highly effective in most patients with paroxysmal AF.⁵⁻⁷ However, some patients with paroxysmal AF and nearly all patients with persistent and long-lasting AF require an additional substrate modification to improve the clinical outcome, suggesting that the mechanisms beyond the PVs also contribute to the perpetuation of AF in these patients.⁸⁻¹⁰ The most commonly used method of signal-based substrate modification is the targeting of complex fraction-

ated atrial electrograms (CFAEs).⁹ From an experimental study¹¹⁻¹³ and the clinical setting,¹⁴ the consistent observation of high frequency and spatiotemporally periodic waves strongly supports a functional reentry responsible for AF maintenance. However, it still remains unclear how to identify the critical arrhythmogenic atrial substrate.

In this article, we review the current evidence from basic science and the clinical experience in regard to the differences in the atrial substrate properties in patients with different types of AF.

Overview of the Atrial Substrate

Underlying Pathophysiologic Mechanism of the Atrial Substrate

Pathologic alterations in various disorders, such

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as ischemic heart disease, valvular heart disease, inflammatory heart disease, cardiomyopathies, systemic hypertension, and hormonal diseases as well as cardiac aging predispose to AF.¹⁵ Histologic and ultrastructural examinations of the atrial tissue in such conditions have reported that a focal or diffuse injury to the atrial myocardium can cause inhomogeneity of the atrial repolarization or conduction leading to the induction of AF.¹⁶ In the experimental studies, investigators have developed an assortment of large animal models in an attempt to recapitulate AF as observed in various clinical settings. In a rapid atrial pacing model, Wijffels et al. reported that sustained AF leads to a shortening of the atrial effective refractory period and progressive shortening of the wavelength of the atrial impulse.¹⁷ This observation of tachycardia-induced electrical remodeling creating a substrate for persistent AF, led to the concept that "AF begets AF". Moreover, several investigators demonstrated atrial contractile remodeling, which is a depressed and slow recovery of the atrial contraction after restoration of sinus rhythm (SR). The mechanisms responsible for the post-fibrillatory contractile dysfunction are not completely determined; however, Yue et al. reported that sustained atrial tachycardia in dogs reduces the L-type Ca^{2+} current (ICa-L), and the reduced ICa-L causes a decrease in the action potential duration (APD) and APD adaptation to the rate.¹⁸ These cellular changes could account for the alterations in the atrial refractoriness. The down-regulation of the ICa-L current may be associated with the atrial contractile dysfunction. Furthermore, structural changes (so-called "structural remodeling") in the response to AF have also been reported in experimental studies. The AF-induced structural changes in the atrial myocytes was reported as an increase in the cell size, loss of the sarcoplasmic reticulum and atrial myofibrils, changes in the mitochondrial shape, perinuclear accumulation of glycogen, alteration in the connexin expression, and increase in the extracellular matrix.¹⁹⁻²² Alessie et al. proposed positive feedback-loops of the cascades of electrical, contractile, and structural remodeling in AF.²⁰ Moe et al. demonstrated that multiple randomly propagating and self-perpetuating "daughter wavelets" act as a mechanism for the perpetuation of AF.²³ Recent observations of the initiation of AF from the pulmonary veins in the clinical setting and the concept of high frequency sources

(i.e. rotors) in experimental and simulation models,¹³ as a result of anisotropic reentry have provided new concepts for understanding the initiation and maintenance of AF. Elimination of arrhythmogenic triggers originating from the PVs appears to work well for paroxysmal AF patients; however, in some of those patients and patients with an increase in the AF duration, the role of the atrial architecture becomes progressively more prominent as atrial remodeling advances. Therefore, AF ablation has attempted to move beyond the isolation of the PVs into the modification of the AF substrate, especially in patients with persistent and long-lasting AF. Complex electrical signals are seen during AF, and each are related to the complex structure and electrical substrate of the atrium. During AF, these signals can be observed using both "time-domain (fractionation)" and "frequency-domain (spectral)" mapping.

Signal Analysis of the Local Electrograms During SR and AF---CFAE, DF, AF Nest, And Non-Linear Signal Analysis

Konings et al., for the first time, described the features of the fragmented electrograms in AF, which were largely identified in regions of either slow conduction or locations where wavelets pivoted.²⁴ Then, Nademanee et al. defined CFAEs as local electrograms with two or more deflections, continuous activity over a 10-second recording, or a mean cycle length of <120 ms over a 10-second recording, and they proposed that the CFAE-targeted ablation of AF was an effective strategy for maintaining SR.^{9,25} Kalifa et al. found that the periphery of high-frequency AF drivers is the area where most fractionation occurs.¹³ According to these studies, areas of CFAEs are considered to be sites of slow conduction, conduction block, wavefront collisions, or anchor points for reentrant circuits that can perpetuate AF. Moreover, CFAEs may also indicate fibrillatory conduction and sites of autonomic innervation.²⁵⁻²⁷ On the other hand, some CFAE sites may reflect passive atrial activation; therefore it is likely that not all CFAE sites need to be targeted for catheter ablation. In Chen's laboratory, they proposed continuous CFAEs defined as having a mean fractionation interval (FI) of <50 msec over 6 seconds.²⁸ The consistency of the continuous CFAEs was investigated in that study. Furthermore, it could be important for

identifying critical CFAE regions, and a continuous CFAE-targeted ablation following PV isolation could be more effective in maintaining SR than PV isolation alone for chronic AF patients.¹⁰

A frequency-domain analysis of the atrial electrograms using the fast Fourier transform method filters out “noise” and identifies the different frequency components. The resultant power spectrum is a graph of dominant frequencies (DF) that are present within the period of the duration they are collected. The DF of the electrograms represents the frequency of the highest power in the spectrum. Assuming an appropriate pre-treatment of filtering is applied, the DF is related to the inverse of the average cycle length. Therefore, the purpose of the frequency analysis is to map the mean activation rate of seemingly chaotic signals during AF. The sites with the highest DFs were considered to be the drivers of the AF during the analysis of the intracardiac fibrillatory signals throughout the right and left atria.

An alternative approach is to use the spectral analysis to characterize the sinus electrograms, based on the consistency of the sinus electrograms over time. Previous studies showed that the abnormal atrial sites are characterized by fractionated electrograms in the time-domain signals and the high frequency peaks in the frequency spectra during SR.²⁹⁻³³ According to a previous study, the high DF sites (so-called “AF nest”) were identified by visual inspection of the frequency spectra, especially in the high frequency range of >80 Hz.³⁴ Lin et al. applied 30 Hz high pass filtering to exclude the fundamental peaks to highlight the corresponding high DF sites of the abnormal atrial substrate.³⁵ The optimal detection of AF nests and the underlying pathophysiologic mechanism need to be clarified in future studies.

Recently, Lin et al. proposed a new concept of a “non-linear analysis method (newly-developed beat-to-beat nonlinear measurements of the repetitiveness of an electrogram over 6 seconds)” to quantify the organization of fibrillation electrograms to differentiate the culprit CFAEs from bystanders (passive CFAE sites).³⁶ All linear analysis technologies (dominant frequency and fractionation interval) may not be sufficient modalities to localize culprit atrial substrates for now because there are some crucial restrictions as-

sociated with those analysis methods. The data must be strictly periodic or stationary; otherwise, the results will make little physical sense. Therefore, further research in this field will be required.

Paroxysmal Atrial Fibrillation

Activation and Voltage Mapping During Sinus Rhythm

A previous experimental study demonstrated that the tachycardia-induced shortening and maladaptation of the atrial effective refractory period and increased inducibility of AF after chronic atrial pacing recovered faster in the right atrium (RA) than in the left atrium (LA), which suggests the possibility of discordance of the bi-atrial substrate.³⁷ In the clinical setting, Chang et al. reported that the LA had a lower voltage, higher heterogeneity of the voltage, and higher low voltage zone (LVZ) and scar area index compared with those in the RA.³⁸ The regional distribution of the scar in the LA differed between the paroxysmal and persistent AF patients; however no significant difference in the regional distribution of the scar area in the RA was observed between the two groups. The scar or LVZ in the LA forms an area where wave break occurs, which may result in the formation of a conduction disturbance and intra-atrial reentry by serving as an anisotropic barrier. A conduction disturbance caused by the heterogeneity of the LA substrate further contributes to the dispersion of the refractoriness and the heterogeneity of the recovering tissue, which was considered to favor the induction and maintenance of AF. In patients with AF, impulses initiated by a focal source from the PVs propagate into the LA. The heterogeneously recovered tissue contributes to the formation of sustained rotors in the LA, which may generate high frequency impulses that proceed to the remainder of the atria with fibrillatory conduction.^{39,40} Therefore, an increase in the heterogeneity of the LA substrate may facilitate the initiation and stabilization of AF, and the RA is passively activated by fibrillatory conduction. On the other hand, previous studies demonstrated that AF initiating triggers from the RA (superior vena cava, coronary sinus ostium, or crista terminalis) and an RA substrate were important in some AF patients.^{7,41,42} Furthermore, the conduction abnormalities associated with atrial fibrosis were important in stabilizing the reentry of AF, and the fibrotic chang-

es were more intense in the LA than in the RA.⁴³ Atrial fibrosis and scarring disturb the intra-atrial conduction, which may contribute to the increased propensity for atrial arrhythmias.^{44,45} A recent study demonstrated that delayed-enhancement magnetic resonance imaging (DE-MRI) provides a noninvasive method to detect pathological regions of LA tissue associated with AF.⁴⁶ In addition, the regions of enhancement on the DE-MRI correlated with the low-voltage regions on the electroanatomical mapping. Similar to the previous studies, the preexistence of LA fibrotic tissue and scarring are considered independent predictors of procedural failure and eventual AF recurrence.³³ Stiles et al. also reported that the changes in the atrial voltage and intra-atrial conduction may represent essential contributors to the “second factor” in paroxysmal AF patients, which has an important role in the further development and progression of AF.⁴⁷

Relationship Between Pulmonary Vein Triggers and the Atrial Substrate

Since the seminal observation that PVs may act as sources triggering ectopy for AF, PV isolation has become a cornerstone of the invasive therapy for patients with paroxysmal as well as persistent AF.^{5,6} However, the development of AF requires a “trigger” and also an anatomical substrate capable of both initiating and perpetuating AF.⁴⁸ Areas of CFAEs and high DF sites have been proposed as important regions for maintaining AF. A recent study reported that PV isolation plus a CFAE targeted ablation in high burden paroxysmal AF patients had a significantly higher freedom from AF than PV isolation or CFAE targeted ablation alone.⁴⁹ Thus, identifying the atrial substrate electrograms may allow for a targeted ablation to improve the success rate.

A previous animal study and computer simulation models indicated that the wavefront arising from shifting of high DF rotors and peripheral fibrillatory conduction through an inhomogeneous atrial substrate gave rise to the fibrillatory conduction.^{11, 50,51} They demonstrated that the highest incidence of wavebreaks and the beat-to-beat variability in the direction and velocity of the propagation are associated with highly fractionated signals located at the boundaries of the high DF regions. Several clinical studies reported that CFAEs were observed adjacent to areas of high DF activation in patients with paroxysmal and non-paroxysmal AF.^{10,52}

Therefore, a CFAE targeted ablation following PV isolation had a better clinical outcome in paroxysmal AF patients with still inducible AF after PV isolation and non-paroxysmal AF patients,^{49,53,54} however, the additional efficacy remained controversial in the patients with paroxysmal AF.⁵⁵ Lin et al reported that the highest DF was located within the arrhythmogenic PV or its ostium in the PV-AF patients, and those patients also had a significant frequency gradient from the PV ostium to the LA.⁵⁶ Similarly, in the recent study, Suenari et al. demonstrated a close relationship between the arrhythmogenic PVs and the critical atrial substrate near the PVs manifesting abnormal fibrillatory electrograms.⁸ Furthermore, the most fractionated regions were mostly located in the periphery of the high DF regions. All of the critical atrial substrates identified by the automatic algorithm of the electrogram analysis were located less than 15 mm from the PV, indicating the possible need to extend the circumferential PV isolation in patients with paroxysmal AF.

Persistent and Long-lasting Atrial Fibrillation

Distribution of the Atrial Abnormal Substrate in Both Atria

Nademanee et al. investigated the regional distribution of the CFAEs in both atria.⁹ According to that study, 45% of the patient population had CFAEs in three or more areas. In those patients, the CFAEs were located in the inter-atrial septum (83%), PVs (67%), left atrial roof (61%), proximal coronary sinus and its ostium (59%), cavotricuspid annulus (31%), mitral annulus (24%), inferolateral aspect of the RA (7%), and RA-SVC junction (4%). Another study demonstrated that all the non-PV ectopies were located in the continuous CFAE regions (FI <50 msec).⁵⁷ Moreover, 25% and 57% of the atrial continuous CFAEs in the LA and RA exhibited corresponding non-PV ectopic sites, respectively. Although CFAE mapping and ablation were usually performed in the LA first, it was not extensively distributed in the RA. Experimental models showed that organized and high-frequency rotors are non-stationary and continually drift within a certain distance.⁵⁸ However, regions of CFAEs have been shown to be spatially and temporarily stable in the human LA during >6 second

electrogram recordings.²⁸ Thus, an anatomical atrial substrate perpetuating AF appears to be spatially stable over time within individual patients. Therefore, limited ablation of continuous CFAEs could lead to the prevention of an extensive destruction of the atrial CFAEs with longer FIs.

Verma et al. recently reported that the DF and CFAE regions overlapped only about 50% of the time; however, AF termination sites occurred at these overlapping sites where the DF was greater than the mean DF values for the map.⁵⁹ In another study, the spatial distribution of the fractionated activity was related to the location of the maximal DF sites.⁶⁰ Moreover, the most consistent CFAE activity was observed near the maximal DF sites and the core of the widely distributed continuous CFAEs correlated with the maximal DF sites. That could be due to increased meandering of AF rotors, boundaries of fixed high frequency sources, or an inhomogeneous atrial substrate without any high frequency sources in the vicinity. Since the prospective ablation of DF sites plus a PV antral isolation did not improve the 1-year success rate over a PV antral isolation alone in the study by Verma's laboratory, further multicenter, randomized trials will be required to find an optimal ablation strategy for non-paroxysmal AF patients.

Identification of the Critical Atrial Substrate

As described earlier, previous studies demonstrated the efficacy of adjunctive CFAE-targeted ablation in addition to circumferential PV isolation.^{49, 54} Nademanee et al. first described a high success rate of a CFAE-targeted ablation without a PV isolation.⁹ Since then, CFAE-targeted ablation has been performed for CFAE sites with cycle lengths of less than 120 msec by visual assessment or by automated computerized algorithms. In the original description of the technique, an average of 64 ± 36 sites were ablated per patient. At the one-year follow-up, 88% of the non-paroxysmal AF patients in that study were free of arrhythmias and symptoms with or without antiarrhythmic drugs.⁹ According to the recent meta-analysis studies, adjuvant CFAE ablation in addition to PVI increases the rate of long-term SR maintenance in non-paroxysmal AF patients.^{61, 62} However, the long-term success rates of electrogram-guided ablation varied among the different investigators

(Table 1).^{9, 54, 59, 63-70} The causes of this discrepancy may arise from the different definitions of targeted CFAEs and different strategies for the CFAE ablation (RF application settings, targeted chamber, and end point of the procedure) in each laboratory. For identification of the critical atrial substrate, most of the worldwide laboratories used a CFAE definition in accordance with Nademanee's report.⁹ On the other hand, Chen's laboratory adopted a mean fractionation interval of the local electrogram of less than 50 msec over a 6 second recording duration by automated computerized algorithms as continuous CFAEs because the critical CFAEs related to the AF maintenance should be continuous and stable over time.²⁸ Even though the limited ablation of the continuous CFAE areas was performed, it had a limitation of the SR maintenance rate in patients with persistent and long-lasting persistent AF (78% and 70%, respectively).¹⁰ Therefore, we need to search for the next breakthrough in signal analysis in order to be able to differentiate the critical CFAE sites from bystanders, such as with non-linear analysis methods as described earlier. Additionally, the recent report by Narayan et al. has also been provocative in view of the concept of rotors in humans during mapping of AF.⁷¹

In the experimental studies, high resolution optical mapping allowed the observation of high-frequency periodic activity that transmitted outward to the remaining atrial tissue, leading to fibrillatory conduction. A retrospective analysis showed that the DF sites corresponded to the successful ablation site.^{39, 72} The highest DF could be identified around the stationary reentrant circuits in the atrial substrate. Thus, an ablation strategy guided by a frequency analysis may be a better way for finding the critical substrate in the maintenance of AF.⁷³ Aienza et al. prospectively applied real-time DF mapping and ablation of DF sites in AF patients.¹⁴ However, ablation of high DF sites did not provide a sufficient AF termination rate, and was only 53% in the paroxysmal and 11% in the persistent AF patients. Furthermore, they performed PV isolation in all patients after a DF-guided substrate modification. In that study, the presence of an inter-atrial DF gradient indicated a better response to this procedure, and the end-point of the substrate modification was the elimination of the DF gradients between the LA and RA. These studies emphasized the importance of extensive mapping of the DFs and elimination of these foci

Table 1 Results of Electrogram-guided Ablation in Patients with Atrial Fibrillation in the Worldwide Laboratories

Author	Year	N	Target Chamber	Ablation Procedure	RF Application Time (min)	Procedure Time (min)	AF Termination	Follow Up	Long-Term SR Maintenance Rate
Nademanee et al.	2004	121	LA, CS, RA	CFAE	–	186	91%*	12	76% (S)§, 91% (M)§
Oral et al.	2007	100	LA, CS	CFAE	36	206	16%†	14±7	33% (S)‡, 57% (M)‡
Oral et al.	2009	50	LA, CS	PVAI+CFAE	87	329	18%†	10±3	36% (S)‡, 60% (M)‡
Schmitt et al.	2007	66	LA, CS, RA	PVI+CFAE	66	326	80%†	12±3	54% (S)
O'Neill et al.	2009	153	LA, CS, RA	Stepwise ablation	88	255	85%†	34 (28-40)	48% (S)§, 89% (M)§
Elayi et al.	2008	49	LA, CS, RA	PVAI+CFAE	–	239	74%†	16±1	61% (S)§, 80% (M)‡, 94% (M)§
Estner et al.	2008	35	LA, CS, RA	PVI+CFAE	–	367	66%†	19±12	51% (S)‡, 74% (M)‡
Verma et al.	2011	30	LA	DF+PVAI	77	249	14%†	12±2	57% (S)‡
Lin et al.	2009	30	LA, CS	PVI+line+CFAE	103	181	47%*	14±7	70% (S)§, 83% (M)§
Seitz et al.	2011	22	LA, CS, RA	CFAE±PVI	81	258 min	95.4%†	12±6	82% (M)§
Iriki et al.	2011	100	LA, CS, RA	CFAE	55 (PAF), 66 (Per AF), 74 (Long-standing AF)	222 (PAF), 240 (Per AF), 278 (Long-standing AF)	98%* (PAF), 80%* (Per AF), 55%* (Long-standing AF)	23±5	65% (PAF) (S)§, 54% (Per AF) (S)§, 45% (Long-standing AF) (S)§

LA, left atrium; RA, right atrium; CS, coronary sinus; RF, radiofrequency; SR, sinus rhythm; PVI, pulmonary vein isolation; PVAI, PV antral isolation; CFAE, complex fractionated atrial electrogram; DF, dominant frequency; PAF, paroxysmal AF; Per AF, persistent AF; *SR conversion; †SR conversion or regularization in atrial tachycardia; S, single ablation procedure; M, multiple ablation procedures; ‡without antiarrhythmic drugs; §with antiarrhythmic drugs

was important for the long-term maintenance of SR. Lin et al. recently demonstrated that the fractionated sites in the vicinity of the highest DF were frequently associated with AF procedural termination compared to the other CFAE sites.¹⁰ This data showed that DF mapping could be an adjunctive tool to identify the critical CFAEs especially when a CFAE ablation was applied for substrate modification after a PV isolation.

Implications for AF ablation

Electrogram approaches guided by DF and CFAE mapping were widely applied for atrial substrate mapping and ablation.^{9, 10, 52} A recent study demonstrated the close relationship between arrhythmogenic PVs and high DFs and the fractionated “rotors” around them.⁸ These findings could

be reasonable for understanding the mechanism of the maintenance with regard to the initiators in patients with paroxysmal AF. Since with the current balloon catheters, such as the cryoballoon, laser, and ultrasound balloon catheters, it has been reported that electrical PV isolation was achieved at the level of the PV ostia and not in the antral regions, that method could be beneficial only for paroxysmal AF patients.⁷⁴ On the other hand, circumferential PV isolation is well known for achieving a better outcome than segmental ostial PV isolation.⁷⁵ The reason may be that wide circumferential PV isolation results in an acute decrease in the DFs and a reduction in the continuous CFAEs.^{10, 76} The atrial substrate with CFAEs was considered to be the maintainer of AF. These fractionated sites were characterized by non-linearity and being non-stationary both spatially and temporally. Some inves-

tigators applied the organization index or harmonic index to quantify the degree of fractionation.⁷⁷ The organization and harmonic index (the width of the DF peaks) represent the irregularity of the DF value over time and do provide some information about the consistency of the DF. However, the spectral morphology index (DF and harmonic index) may be overcome by the presence of chaotic signals, presented in the background of the power spectra. A previous study demonstrated the limitation of the regularity index in the determination of the degree of fractionation.⁷⁸ In fact, in seemingly chaotic fibrillatory signals, identification of the DF may be ambiguous and would be technically challenging. Furthermore, the signal analysis based on DF gradients provides limited value when the regional DF gradient was limited in patients with non-paroxysmal AF. It may not be suitable to use the linear methodology for the delineation in those highly complex electrograms. In clinical practice, electrograms with a regularity index of less than 0.2 are usually excluded from a DF analysis.⁷⁹ In the future, nonlinear processing of highly disorganized fractionated activity of the intracardiac recording may allow for a more targeted approach to identify the critical atrial substrate in patients with long-lasting AF.

Conclusions

Substrate mapping is emerging as a technique for guiding the electrogram-guided atrial ablation of AF. Recent developments in the technologies of 3D electroanatomical mapping systems and electrogram analysis software have clarified the differences in the atrial substrate properties in patients with paroxysmal and non-paroxysmal AF. The high density recording of electrical signals from both atria will make it possible to enhance our knowledge of the pathogenetic mechanisms of AF and improve the AF ablation technique. According to previous studies, the area of the CFAEs may indicate sites of slow conduction, conduction block, wavefront collisions, or anchor points for reentrant circuits that can perpetuate AF. On the other hand, a part of those areas may include passive and bystander CFAEs, which could lead to extensive and an unnecessary atrial substrate modification. Moreover, the regional DF distribution could be homogeneous in patients with long-lasting AF. This also may cause difficulty in identifying the high DF sites. The catheter ablation strategy for pa-

tients with non-paroxysmal AF has evolved into an electrogram-guided ablation followed by PV isolation, but a hybrid method together with other methodologies remains to be seen.

Disclosures

No disclosures relevant to this article were made by the authors.

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