Relationship between automatically detected complex fractionated electrograms and sites of termination of long-standing persistent atrial fibrillation during catheter ablation

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Background: Complex fractionated atrial electrograms (CFAE) may provide a target for ablation of persistent atrial fibrillation (AF). This study evaluated relationship between the automatically detected CFAE in the atria and the sites of long-standing persistent AF termination during ablation.
Methods: Fifty consecutive patients underwent a stepwise ablation for long-standing persistent AF. Left atrial (LA), right atrial (RA), and coronary sinus (CS) electroanatomic maps with automatically detected CFAE were obtained before ablation. Stepwise ablation with the ideal endpoint of sinus rhythm restoration was subsequently performed using plain electroanatomic maps. The relationship between CFAE sites and AF termination sites was retrospectively analyzed in 38 patients in whom ablation terminated AF.
Results: There were 70 LA CFAE sites, 48 RA CFAE sites, and 20 CS CFAE sites found in 35 (92 %), 30 (79 %), and 19 (50 %) patients, respectively. Mean distance between the AF termination site and the closest CFAE site was 21.7±17 mm. Distance between the AF termination site and the closest CFAE site ≤ 10, or 11–20 mm was found in 11 (29 %), and 10 (26 %) patients, respectively. AF termination was achieved after ablation of 85 ± 28 % LA CFAE sites, 58±28 % CS CFAE sites, and 16 ± 33 % RA CFAE sites.
Conclusions: Although the CFAE sites and AF termination sites did not directly correlate in a majority of the patients, most of the LA CFAE sites and more than half of the CS CFAE sites had been targeted before AF termination, suggesting rather cumulative effect of CFAE ablation.

Key words: atrial fibrillation, long-standing persistent, catheter ablation, complex fractionated atrial electrograms.

Vztah mezi automaticky detekovanými komplexními frakcionovanými elektrogramy a místy ukončené dlouhodobé perzistentní fibrilace síní při katetrové ablaci

Úvod: Komplexní frakcionované síňové potenciály (CFAE) mohou poskytnout vodítko při ablaci perzistentní fibrilace síní (FS). Tato studie hodnotila vztah mezi automaticky detekovanými CFAE v srdečních síních a místy, v nichž došlo k ukončení dlouhodobé perzistentní FS ablací.
Metodika: Padesát konsekutivních pacientů podstoupilo stupňovanou ablaci dlouhodobé perzistentní FS. Před ablací byly vytvořeny elektroanatomické mapy levé síně (LS), pravé síně (PS) a koronárního sinu (CS) s automaticky detekovanými CFAE. Stupňovaná ablace se snahou obnovit sinusový rytmus jako ideálním cílovým momentem výkonu se provedla s použitím jednobarevné elektroanatomické mapy. Vztah mezi místy CFAE a místy ukončení FS byl retrospektivně analyzován u 38 pacientů, u nichž byla FS terminována ablací.
Výsledky: Bylo nalezeno 70 míst CFAE v LS, 48 míst CFAE v PS a 20 míst CFAE v CS u 35 (92 %), 30 (79 %), respektive 19 (50 %) pacientů. Průměrná vzdálenost mezi místem ukončení FS a nejbližším místem CFAE byla 21,7±17 mm. Průměrná vzdálenost mezi místem ukončení FS a nejbližším místem CFAE ≤10, respektive 11–20 mm byla nalezena u 11 (29 %), respektive 10 (26 %) pacientů. Ukončení FS bylo dosaženo až po ablaci 85±28 % míst CFAE v LS, 58±28 % míst CFAE v CS, a 16±33 % míst CFAE v PS.
Závěr: Ačkoli u většiny pacientů místa CFAE přímo nekorelovala s místy ukončení FS, většina míst CFAE v LS a více než polovina míst CFAE v CS byla cílena před dosažením terminace FS, což naznačuje spíše kumulativní efekt ablace CFAE.

Klíčová slova: fibrilace síní, dlouhodobá perzistentní, katetrová ablace, komplexní frakcionované síňové potenciály.

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Introduction

Arrhythmogenic substrate and sources of long-standing persistent atrial fibrillation (AF) outside the pulmonary veins (PVs) have not been fully understood (1–5). Selective cluster ablation of complex fractionated atrial electrograms (CFAE) sites has become a routine part of a stepwise ablation approach capable of AF termination in a substantial proportion of the patients (1, 3, 5). On the other hand, linear ablation targeting typical regions of CFAE may also be effective in AF termination (4). Sites of CFAE within the atria can be automatically detected and coded in color on the 3D electroanatomical map and serve as a more objective guide for navigating ablation lesions (6–8). However, what are the typical locations of CFAE in long-standing persistent AF, and which CFAE represent a specific AF source remains unknown (Figure 1).

This prospective study was aimed at investigating the hypothesis that ablation consisting mainly of wide area PV isolation and additional linear ablation would target a majority of CFAE sites, and that the sites of AF termination would spatially correlate with the CFAE sites automatically detected on the preablation electroanatomical maps.

Methods

Study Population

Ablation was performed in 50 consecutive patients aged 34–74 years with symptomatic long-standing persistent AF lasting >12 months without intervening SR, refractory to amiodarone, and resistant to, or recurring within 7 days after electrical cardioversion. Incapacity, dyspnea, fatigue, and sweating were the dominating symptoms. Patients with severe left ventricular dysfunction due to primary structural heart disease were not included. The study population consisted of 38 (76 %) patients, in whom AF was terminated by ablation, and in whom the relationship between the sites of AF termination and SR restoration and the sites displaying CFAE was analyzed. Baseline clinical characteristics are shown in Table 1. There were no baseline differences between the patients with AF termination versus non-termination. Amiodarone was taken immediately before ablation in 18 (47 %) patients with AF termination and in 5 (42 %) patients without AF termination (p = 0.83). The local ethics committee approved the study, and all patients gave written informed consent.

Electrophysiological study and electroanatomic mapping

Warfarin was discontinued and replaced by low-molecular-weight heparin for 5 days prior to ablation. Laboratory tests and transthoracic/transesophageal echocardiography were performed < 48 hours prior to the ablation procedure.

For the electrophysiological study, a 10-pole catheter (Daig, St. Jude, Minnetonka, MN, USA) was positioned in the coronary sinus (CS), and a 10-pole ring catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) and a mapping/ablation catheter (NaviStar ThermoCool, Biosense Webster) were inserted via two 8 F transseptal sheaths (Mullins fixed curve, Daig, St. Jude) in the left atrium (LA) and PVs. Heparin was given to maintain activated clotting time of 300–400 seconds.

Surface electrocardiograms and bipolar endocardial electrograms were filtered at a band-pass setting of 30–500Hz and recorded digitally (Cardiolab System, Prucka Engineering, Sugar Land, TX, USA). Detailed pre-ablation left atrial (LA), right atrial (RA), and coronary sinus (CS) electroanatomic maps were acquired using the CARTO system (Biosense Webster). Efforts were made to acquire dense maps of equally distributed points. The electrode-tissue contact was verified by the electrogram, fluoroscopy and intracardiac echocardiography. To acquire a single point, the mapping catheter was kept at each site in a stable position for at least 3 seconds. Sites displaying CFAE were re-visited to prove the CFAE stability.

Automated CFAE mapping

We used the CFAE Software Module (Biosense Webster) providing online automated identification and 3D visualization of CFAEs and the protocol of CFAE acquisition suggested earlier by Calo, et al. (8). At each mapping site, a 2.5-second window of bipolar electrogram was analyzed. Low amplitude high-frequency electrograms were identified by tagging peak voltage of bipolar deflections under the lower threshold 0.05 mV to exclude noise. Voltage peaks greater than this threshold but lower than the upper threshold 0.15 mV were subsequently analyzed. Then the intervals between successive peaks within the voltage window of 0.05 and 0.15 mV were calculated. Finally, inter-peak intervals that fell within a programmable duration 70–120 ms were identified, and the number of such intervals during the 2.5 second sampling window were summed as the interval confidence level (ICL). Sites exhibiting greater ICL, i. e. greater number of short intervals between low amplitude multi-deflection complexes reflect more frequent and more repetitive CFAE. Typically, the sites with ICL ≥20 intervals have been arbitrarily considered as high ICL and the sites with ICL 10–20 intervals as medium ICL (8). Because no ICL ≥20 intervals was found in a substantial proportion of our patients, we chose a more conservative cutoff for the ICL >10 and coded these areas as CFAE in red color.

Catheter ablation

Radiofrequency energy was applied with a Stockert generator (Biosense Webster). We used irrigation of 17–30 ml/min (0.9 % saline) through a Cool Flow pump (Biosense-Webster), and temperature and power limits of 42°C and 35 W; respectively, irrigation and power were limited to 20 ml/min and 20–25 W inside the CS.

Although the preablation mapping was performed with the knowledge of CFAE sites to ensure precise CFAE mapping, ablation itself was performed using plain electroanatomic maps without directly looking at the CFAE maps and guiding the ablation lesions by the CFAE information. Principles of stepwise ablation strategy have been described elsewhere (4, 9). Briefly, wide PV antra isolation, LA appendage (LAA) -left PVs ridge, (postero) lateral mitral isthmus, LA roof, and cavo-tricuspid isthmus ablation were the mandatory steps that were always finalized irrespective of the current rhythm.

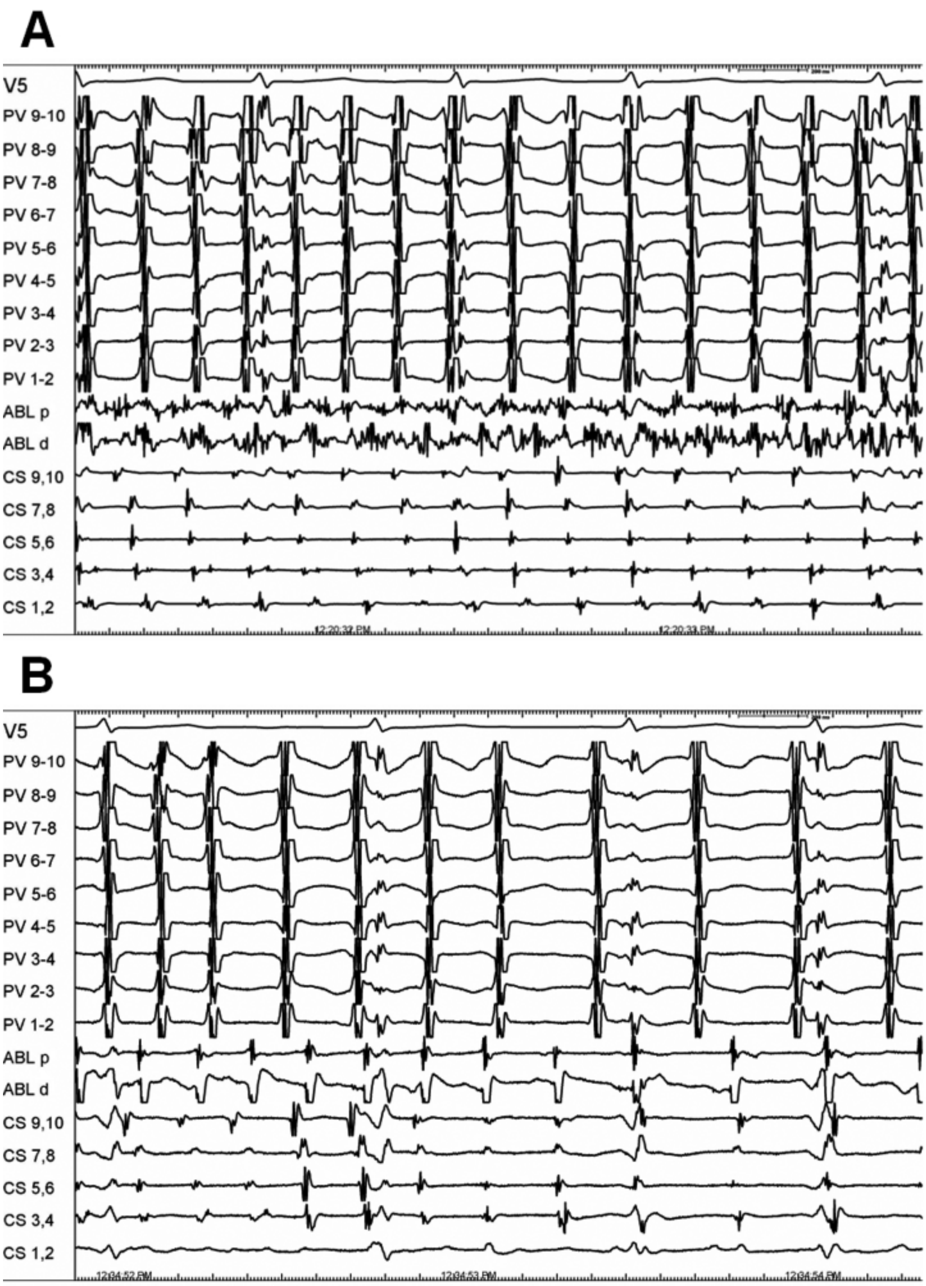
When AF continued, additional LA lines were added. Lines included posteroseptal mitral isthmus ablation connecting right lower PV with the posteroseptal mitral annulus, and anterior line from the anterior segment of the mitral annulus upwards along the septal aspect of the LAA towards the LA roof, leaving, however, the Bachmann's bundle route preserved in order to prevent delayed LAA activation or isolation (9). If AF continued, the CS was isolated. It was not targeted if AF was terminated/SR was restored and full mitral isthmus block was achieved by prior endocardial ablation, and if no ectopic activity arose from this region. Finally, in patients with continuing AF, RA inter-caval line connecting superior and inferior venae cavae in the posterior septum (10). Following these lines, conventional electrogram-guided ablation using the plain CARTO map might follow to target remaining fast activities or sites of activation gradient.

Table 1. Baseline characteristics

	Patients with terminated AF (n = 38)
Age (years)	59 ± 9 (34–74)
Females	6 (16 %)
Persistent AF duration (months)	31 ± 18 (13–91)
Hypertension	20 (53 %)
Diabetes mellitus	3 (8 %)
Stroke/TIA	10 (26 %)
History of LV dysfunction	6 (16 %)
CHADS2	1.3 ± 1.3 (0–4)
Height (cm)	176 ± 9 (155–198)
Weight (kg)	95 ± 15 (51–138)
Body mass index	30.5 ± 3.9 (19.4–41.7)
LA A-P diameter (mm)	48 ± 5 (38–58)
LV ejection fraction (%)	55 ± 9 (29–67)

Data show as mean ± standard deviation or proportions (%). AF = atrial fibrillation; A-P antero-posterior; LA = left atrium; LV = left ventricle; TIA = transient ischemic attack

Figure 1. A. Example of continuous fractionated electrogram recorded by the distal and proximal bipole of mapping/ablation catheter (ABL d, ABL p). Activity registered simultaneously by the 10-pole catheter in the coronary sinus (CS 1,2-CS 9,10), and by the ring catheter (PV 1-2 to PV 9-10) placed within the left atrial appendage is relatively organized. B. Ablation at the site of CFAE later terminated AF, i. e. converted AF into regular monomorphic atrial tachycardia thus suggesting ablation of a specific AF driver. Speed of ECG recording = 100 mm/s



The stepwise ablation strategy was pursued until AF termination, i. e. AF conversion into atrial tachycardia (AT) or directly into SR. Converted AT (macroreentry or localized source) was identified by means of activation and entrainment mapping. If ablation of AF/AT failed to restore SR, intravenous propafenone, overdrive pacing, and electrical cardioversion were successively applied. At the end of the procedure, PV antra isolation was confirmed by the ring catheter and efforts were made to achieve conduction block (if not already present) at cavo-tricupsid isthmus, (postero) lateral mitral isthmus, and roof line, according to standard differential pacing criteria. The posteroseptal mitral isthmus, LA anterior, and RA inter-caval lines were checked for electric silence along the lesions.

Measurement of CFAE and relationship with AF termination sites

Total surfaces of LA and RA were automatically calculated by the CARTO software (function "Area measurement"). Surface of the CS was not calculated for variations in the extent and completeness of CS mapping. Surface of each CFAE site was determined automatically by circumscribing the CFAE area with a caliper and coded in red color (function "Area measurement"). Numbers and surfaces of CFAE sites within each atrium were calculated. Finally, the shortest distance between the site of AF termination/SR restoration and the border of the nearest CFAE site was measured (function "Distance measurement"). CFAE sites within the distance ≤10 mm and 11–20 mm, respectively, to the site of AF termination/SR restoration were considered as corresponding with, or abutting the site of AF termination/SR restoration.

Postablation management

Heparin was stopped after the procedure, and low-molecular-weight heparin was administered until warfarin reached its full therapeutic effect. Warfarin was stopped after 6 months in patients with stable SR, preserved LAA function (generally, outflow velocity ≥40 cm/s), and without other conditions indicating permanent anticoagulation. There was a tendency to avoid re-initiation of antiarrhythmic medication; however, it was often resumed to stabilize SR in the early postablation course.

Repeat ablation was allowed after 6 months. PVs were re-isolated and incidental gaps in linear lesions (specifically roof line, lateral mitral isthmus and CTI) were closed, even if passive in the recurrent clinical arrhythmia mechanism. At the end of the repeat procedure, arrhythmia non-inducibility was tested by incremental pacing up to 300 bpm from the CS (unless fully isolated) and LAA up to 300 bpm.

Follow-up

Patients were seen at the outpatient department at 6 weeks, 3, 6, 9, and 12 months, and then every 6 months after the ablation with additional phone contacts if necessary. ECG documentation consisted of 12-lead ECG recordings at every visit and interim visits at local cardiologists, 24-hour ECG recordings prior to each visit, and 3-week trans-telephonic ECG monitoring every 6 months using an episodic recorder for daily multiple ECG recordings, both random and during symptoms. Patients were further instructed to record symptoms daily into a diary. Arrhythmia recurrence included ECG documented AF/AT, and, to make the outcome evaluation strict, also any history of palpitations suggestive of AF/AT lasting >30 seconds.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared by

Table 2. Sites of AF Termination

Mandatory steps	13 (34 %)
PV isolation	*9*
Roof line	*1*
Lateral mitral isthmus line – LA ridge	*3*
Additional LA lines	7 (18 %)
Posteroseptal mitral isthmus line	*5*
Anterior line	*2*
Coronary sinus ablation/isolation	5 (13 %)
RA inter-caval line	4 (11 %)
Behind fossa ovalis	*2*
Behind coronary sinus ostium	*2*
Conventional electrogram-guided ablation	9 (24 %)
LA appendage base	*1*
LA septum	*8*
Total	38

LA = left atrium; PV = pulmonary vein; RA = right atrium; LA ridge = ridge between left pulmonary veins and appendage

the 2-tailed Student's t-test for independent samples. Categorical variables were expressed as percentages and compared by χ2-test. A p value <0.05 was considered significant. All analyses were performed using the STATISTICA vers.6.1 software (Statsoft, Inc.).

Results

Immediate Ablation Results

Of the 50 consecutive patients, AF was terminated by the first ablation in 38 (76 %) patients and SR was restored in 28 (56 %) patients; via converted AT in 21 patients, and directly from AF in 7 patients. In these latter 7 patients, the ablation steps/sites were wide area right PV isolation 3×, lateral mitral isthmus/ridge between left PVs and LAA 1×, posteroseptal mitral isthmus line (endocardial aspect of proximal CS) 1×, RA inter-caval line close to fossa ovalis (FO) 1×, and LAA upper base 1×. In 10 patients, in whom AF was converted into AT, but SR was not restored by subsequent ablation, SR was finally restored by propafenone and "ovedrive" pacing 6×, and by electric cardioversion 4×. There was no difference in amiodarone use immediately prior to ablation between the patients with SR restored (18/64 %) versus patients without SR restoration (4/40 %) (p = 0.47).

Ablation steps/sites of AF termination are shown in Table 2. Mandatory steps, additional LA lines, CS ablation/isolation, RA inter-cava line, and subsequent conventional electrogram-guided ablation terminated AF in 34 %, 18 %, 13 %, 11 %, and 24 % patients, respectively.

Of the 21 patients, in whom SR was restored via converted AT, right PV ablation converting AF into AT, when continued, subsequently terminated the AT into SR in 4 patients. Further, perimitrial reentry tachycardia was terminated by revisiting lateral mitral isthmus in 3 patients, and by ablation within the lateral CS in another 1 patient, and roof-dependent reentry tachycardia was eliminated by posterior wall ablation in 1 patient. In the remaining 12 patients, the residual AT was designated as localized, and the AT sources were located in the LA posterior wall pertinent neither to the left nor right PV antrum 1x, upper base of the LAA 2×, septal aspect of the LAA base 2×, ridge between the LAA and left PVs 1×, left side of the septum 4×, and right side of the septum 2×.

Ablation procedure characteristics

In the population of 38 patents with AF termination, the first procedure, fluoroscopy, and radiofrequency energy application times were 305±56 (190–390) minutes, 23±6 (11–36) minutes, and 123 ± 32 (68–185) minutes, respectively.

Characterization of CFAE areas

Seventy LA CFAE sites were found in 35 (92 %) patients, 48 RA CFAE sites were found in 30 (79 %) patients, and 20 CS CFAE sites were found in 19 (50 %) patients, respectively. Locations of CFAE are schematically shown in Figure 2 and described in Table 3. The numbers of distinct CFAE sites, and their absolute and relative surfaces within the particular chamber are shown in Table 4. No CFAE was present in 1 patient; Only RA CFAEs were found in another 2 patients (Figure 3).

Relationship between AF termination and SR restoration sites and CFAE sites

Mean distance between the AF termination site and any CFAE site was 46.2±25 (0–105.9) mm. Mean distance between the AF termination site and the closest CFAE site was 21.7 ± 17 (0–67.5) mm. Distance between the AF termination site and the closest CFAE site ≤ 10 mm was found in 11 (29 %) patients; distance between the AF termination site and the closest CFAE site 11–20 mm was present in another 10 (26 %) patients (Figure 4). Among the

Table 3. Location of CFAE Sites (n = 138)

N.	Location	C.	N.	Location	C.
1	Left PV antrum	2 (1 %)	13	LA septum – beneath FO	10 (7 %)
2	Right upper PV antrum	3 (2 %)	14	RA septum around FO	12 (9 %)
3	Right lower PV antrum	4 (3 %)	15	RA – CS ostium area	2 (1 %)
4	LA roof	12 (9 %)	16	CS proximal	9 (7 %)
5	LA posterior wall	3 (2 %)	17	CS posterolateral	8 (6 %)
6	Posteroseptal mitral isthmus	4 (3 %)	18	CS lateral	3 (2 %)
7	Posterolateral mitral isthmus	5 (4 %)	19	Crista terminalis	7 (5 %)
8	Left PV-LA appendage ridge	6 (4 %)	20	RA appendage apex	4 (3 %)
9	Septal base of LA appendage	5 (4 %)	21	Septal base of RA appendage	7 (5 %)
10	Inferior base of LA appendage	3 (2 %)	22	Lateral base of RA appendage	10 (7 %)
11	LA septum in front of right PVs	10 (7 %)	23	Inferior base of RA appendage	1 (1 %)
12	LA septum around FO – limbus	3 (2 %)	24	(Infero) lateral RA wall	5 (4 %)

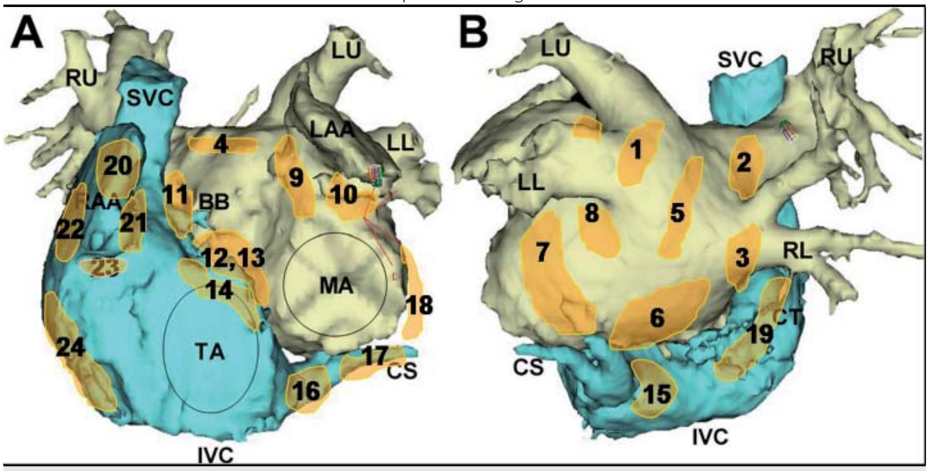
C = count; CS = coronary sinus; FO = fossa ovalis; LA = left atrium; RA = right atrium; PV = pulmonary vein; Posteroseptal/posterolateral mitral isthmus correspond partly to endocardial aspect of relevant segments of coronary sinus

Table 4. Characterization of CFAE Sites

	Left atrium	Right atrium	Coronary sinus
N. of mapping points per A/CS	221 ± 39 (136-304)	178 ± 28 (107-236)	53 ± 14 (23-82)
Atrial volume (ml)	182 ± 40 (119-280)	161 ± 31 (99–221)	NA
Atrial surface (cm2)	197 ± 33 (147-286)	184 ± 26 (115-239)	NA
N. of distinct CFAE sites/pt	1.8 ± 1.2 (0-5)	1.3 ± 0.9 (0-3)	0.5 ± 0.6 (0-2)
Distinct CFAE site surface (cm2)	2.2 ± 1.0 (0-5)	2.1 ± 1.3 (0-5.4)	1.1 ± 1.3 (0-4.1)
Distinct CFAE site surface per A (%)	1.2 ± 0.5 (0-2.4)	1.1 ± 0.6 (0-2.5)	NA
Total surface of CFAE per A (cm^2)	4.3 ± 2.7 (0-9.5)	3.1 ± 2.3 (0-8.4)	NA
Total surface of CFAE per A (%)	2.2 ± 1.4 (0-5.3)	1.7 ± 1.2 (0-3.9)	NA

Data show as mean ± standard deviation (%). A = atrium; CFAE = complex fractionated atrial electrogram; CS = coronary sinus; pt = patient. CS volume and surface and derived variables were not calculated (see text)

Figure 2. Schematic depiction of the CFAE sites (marked in orange and numbered 1 – 24) found in the left (ochre) and right (blue) atria, and coronary sinus (CS) in the anterior (A) and posterior (B) view. See Table 3 for the CFAE occurrence at the particular regions



LAA = left atrial appendage; RAA = right atrial appendage; LU = left upper pulmonary vein; LL = left lower pulmonary vein; RU = right upper pulmonary vein; RL = right lower pulmonary vein; SCV = superior vena cava; IVC = inferior vena cava; MA = mitral annulus; TA = tricuspid annulus

Table 5. Relationship between CFAE and AF Termination Sites

Distance CFAE-AF Termination ≤ 10 mm			Distance CFAE-AF Termination 10–20 mm		
CFAE area	AF Termination	N	CFAE area	AF Termination	N
Right PV	Right PV	1×	Right PV	Right PV	2×
PLMI (CS endo)	PLMI	2×	LA septum	Right PV	1×
PSMI (CS endo)	PSMI	2×	PSMI (CS endo)	PSMI	1×
LA septum	LA septum	2×	LA septum	LA septum	2×
CS proximal	CS proximal	1×	CS posterior	CS proximal	1×
CS ostium (RA)	CS ostium (ICL)	2×	CS proximal	CS proximal	1×
LA septum	RA septum (ICL)	1×	LAA septal base	LAA septal base (ant)	1×
			LAA septal base	LAA upper base	1×

Ant = LA anterior line, CS = coronary sinus; CS endo = endocardial aspect of CS; ICL = termination during creation of inter-caval line; LA = left atrial; LAA = left atrial appendage; PLMI = posterolateral mitral isthmus; PSMI = posteroseptal mitral isthmus; PV = pulmonary vein

CFAE sites corresponding to or abutting the AF termination site in these 21 patients, CS (including endocardial aspect of the vein) dominated in 11 (52 %) cases (details are shown in Table 5).

Of the 9 patients with AF termination by the right PV ablation, the distance between right PV CFAE and right PV ablation site terminating AF ≤ 10 and 11–20 mm was present in only 1 and 2 patients, respectively. In the remaining 6 patients; however, CFAE areas were found relatively close to the right PV antrum (septum in front of the right PVs 3×, left side of the septum around FO 2×, posterior wall between lower PVs 1×).

Mean distance between the SR restoration site and any CFAE site was 49.5 ± 24.3 (0–107) mm. Mean distance between the SR restoration site and the closest CFAE site was 24.5 ± 16.6 (0–60) mm. Distance between the SR restoration site and the closest CFAE site ≤ 10 mm was found in 7 (28 %) patients. Distance between the SR restoration site and the closest CFAE site 11–20 mm and was present in another 5 (18 %) patients.

Of the 4 patients with direct AF conversion into SR by extra PV ablation, the distance between the CFAE and SR restoration site was ≤ 10 mm in 1 patient (posterolateral mitral isthmus/LA ridge) and 10–20 mm in another 1 patient (upper base of LAA).

Of the 12 patients with SR restoration by ablation of a localized AT source, distance between the SR restoration site and the CFAE site ≤ 10 mm was present in 6 patients (left side of the septum 3x, septal base of LAA 2×, LA ridge between left PVs-LAA 1×), and the distance 11–20 mm in another 2 patients (upper base of LAA 1×, right side of the septum 1×).

AF termination was achieved after ablation of 1.6 ± 1.1 (0–5)/85 ± 28 (0–100) % LA CFAE areas, 0.6 ± 0.6 (0–2)/58 ± 28 (0–100) % CS CFAE areas, and 0.2 ± 0.4 (0–1)/16 ± 33 (0–100) % RA CFAE areas.

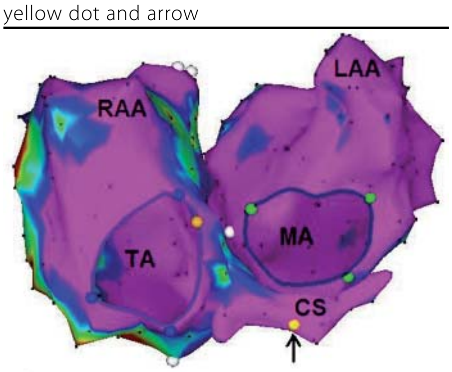
Long-Term Outcome

Ablation was repeated in 29 (58 %) of all 50 patients (1.7 procedures per patient). At the end of the total follow-up time of 38±4 (32–46) months, respectively 30±9 (9–46) months since the last ablation, 47 (94 %) patients remain in stable SR; 45 (90 %) patients remain in SR without antiarrhythmic drugs. In the group of 38 patients with terminated AF, after repeat ablation in 22 (58 %) patients (1.6 procedures per patient), 38 (100 %) patients remain in stable SR, of whom 33 (87 %) patients without antiarrhythmic drugs. Warfarin was discontinued in 36 (72 %) of all 50 patients, and in 30 (79 %) of the 38 patients with terminated AF.

Discussion

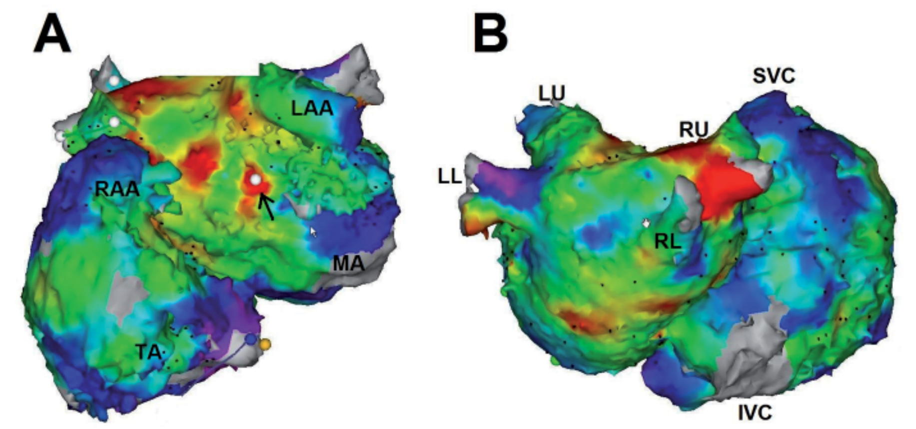
This study of patients with long-standing persistent AF sought to evaluate whether the LA, RA, and CS sites displaying automatically detected CFAE correlate with the sites, where AF was subsequently terminated by the routine stepwise ablation employed without directly utilizing the knowledge of CFAE location. The major findings are as follows: 1) AF was terminated by the stepwise ablation in 76 % of the patients, and SR was restored in 56 % of the patients; 2) A majority of the successful AF termination sites were located outside PVs, and AF directly converted into SR in only minority of the patients; 3) The presence of CFAE areas, as they were defined in this study, varied among the patients, CFAE could also be entirely absent; 4) The sites of AF termination correlated with the sites of preablation CFAE in only minority of the patients; 5) The sites of SR restoration from a converted localized AT source correlated with

Figure 3. Electroanatomic map (roughly left anterior oblique projection) showing left atrium entirely void of CFAE, and right atrium displaying CFAE (coded in red) in the lateral-inferior wall and the septal base of appendage. Left atrial and coronary sinus (CS) stepwise ablation; however, terminated AF without intervening right atrium. AF termination site within CS is marked by the yellow dot and arrow



LAA = left atrial appendage; RAA = right atrial appendage; MA = mitral annulus; TA = tricuspid annulus

Figure 4. Electroanatomic map integrated with the CT scan showing CFAE (coded in red) in the left atrium in the anterior (A) and posterior (B) view. Right atrium is void of CFAE. Mandatory ablation steps including ablation of CFAE within the right upper pulmonary vein, and subsequent ablation of CFAE at the inferior-posterior wall (endocardial aspect of coronary sinus) by the LA posteroseptal line failed to terminate AF. AF was terminated by the incomplete anterior line when crossing CFAE site marked by the white dot and arrow septally to the base of the left atrial appendage



the sites of preablation CFAE in a majority of the patients; 6) Most of the LA CFAE sites and more than half of CS CFAE sites had been targeted before achieving AF termination.

CFAE mechanisms and significance

CFAE ablation as an alternative ablation strategy was first introduced by Nademanee, et al., who defined CFAE as low amplitude multicomponent potentials usually within 0.05 and 0.25 mV that were either continuous or separated by short isoelectric intervals (<120 ms) averaged over a 10-second recording interval (12). It was suggested that CFAE indicate anatomic regions perpetuating reentry. Multiple potential mechanisms by which CFAE may be generated during AF have been provided. They include wavebreak at the periphery of high-frequency rotor (13, 14), local autonomic innervation and activation (15–17), anisotropic conduction or localized reentry (18, 19), or pivot points, wave turning, and slow conduction of a reentry circuit (20, 21). Different electrogram patterns, location stability, or relationship to the adjacent sites may indicate CFAE representing "background" localized sources actively maintaining AF; however, to differentiate CFAE representing active AF drivers from the CFAE that arose from passive fragmentation of activation is difficult.

Visually identified CFAE ablation for persistent AF

In treatment of persistent AF, utilizing CFAE ablation provided inconsistent results. Nademanee, et al. reported termination of persistent AF in 63 % patients (12). Employing purely CFAE ablation in the LA and CS, Oral, et al. terminated chronic AF in only 16 % of the patients (22). In their subsequent study, chronic AF was terminated by the LA/CS ablation in 22 % of the patients, while additional RA CFAE ablation terminated AF in only 1 (3 %) patient (23). Incorporating ablation of visually identified CFAE into the so-called electrogram-guided ablation (together with ablation of the sites of continuous electrical activity, regions displaying local activation gradient, and regions with fast activity) in addition to the PV isolation and mitral isthmus/LA roof lines resulted in AF termination in 87 % patients with persistent AF and favorable long-term success rate (1, 24).

The role of the RA has remained a matter of controversy. Unlike the above mentioned study (23), Rostock, et al. demonstrated persistent AF termination by stepwise ablation in 77 % patients, while it was achieved by the RA ablation in 26 % of the patients. Patient with successful RA ablation displayed a significantly shorter AF cycle length in the RA appendage (RAA) than in the LAA (3). This finding was corroborated by another study which, guided by the RA to LA activation gradient evolving in the course of the LA ablation, identified 30 % of the patients eligible to the RA ablation. RA ablation terminated AF in 55 % of these patients (5). Both the studies identified RAA and RA anterior wall as important RA sites for AF termination.

Linear ablation for persistent AF

Linear catheter ablation for AF, used in the past as the primary ablation strategy, has been largely abandoned following introduction of the PV ablation, although LA roof and lateral mitral isthmus lines survived as inherent part of a stepwise ablation that seems to be required in most of the persistent AF patients to accomplish favorable outcome (25). Additional lines have been recently disputed for its potential proarrhythmic effect; however, they may target (together with PV antra isolation and roof and mitral istmus lines) most of the regions displaying CFAE. On top of that, if complete, their proarrhythmic effect may be lesser than that resulting from cluster electrogram-guided ablation.

In this study, linear ablation was moderately effective in AF termination in 39 % of the patients. PV ablation, or supplementary conventional electrogram-guided ablation terminated AF in 24 % of the patients each, and CS ablation terminated AF in 13 % of the patients. It is possible that some of the septal sources were affected by extensive right PV encircling widely encroaching posterior septum and therefore the effect of PV ablation may be overestimated. Moreover, wide area PV isolation approximating posterior box lesion may have influenced AF more by the cumulative effect on the reentrant substrate than by elimination of a distinct localized source(s).

Automated CFAE detection and spatial CFAE distribution

CFAE detection using automated algorithms provides a tool for CFAE visualization and a potential objective guide for navigation of radiofrequency energy application. Prior study demonstrated that the CFAE software of the CARTO system has a high diagnostic accuracy in identifying CFAE as they are observed visually (8).

In this study, most of the LA CFAE regions were located in the septum, LA roof, around the endocardial aspect of CS, and around the LAA base. In the RA, the most prevalent CFAE regions included the septum, RAA, lateral trabeculated wall, and crista terminalis. This finding is in concord with prior studies using similar settings for automated CFAE detection (6–8). Unlike paroxysmal AF patients, in whom CFAE more often concentrate on the PVs, very few patients with long-standing persistent AF in our study exhibited CFAE located directly in the PV antra, which also agrees with prior experience in persistent AF patients (6–8, 26, 27). This finding may be related to a different persistent AF substrate, which is also supported by the low AF termination rate with mere PV isolation.

Data on automatically detected CFAE in the RA is limited. Unlike one previous study demonstrating prevalent presence of CFAEs in the septum (8), we often found CFAE in the RAA and its surroundings. The difference may relate to different patient populations with lesser atrial structural changes. For comparison, patients in the above mentioned study (8) had persistent AF lasting for shorter time, and displayed smaller LA (132±25 ml) and RA (99±39 ml). Our finding of CFAE around RAA is indirectly supported by previous studies not utilizing automated CFAE detection that demonstrated frequent persistent AF termination by the electrogram-guided ablation around the RAA and RA anterior or lateral wall (3, 5).

Ablation of automatically detected CFAE

Data on ablation guided by automatically detected CFAE is even more limited. In one study, CFAE ablation was performed in 25 patients with persistent AF prior to the PV, roof and mitral isthmus ablation. AF was terminated by the CFAE ablation in only 20 % of the patients. CS and inferior LA wall were the conversion sites. Subsequent PV ablation and roof or mitral isthmus lines terminated AF in 1 and 9 patients (40 %). This finding basically concurs with our study, where PV, roof, and mitral isthmus ablation employed as primary steps terminated AF in 34 % of the patients (7). Similarly, in another study of persistent AF, only 10 % AF termination rate was observed during CFAE ablation following wide area PV isolation (that failed to terminate AF in any patient). In contrast, AF was terminated in 55 % of patients by subsequent roof and mitral isthmus lines (27). Another study of paroxysmal and persistent AF patients showed that 83 % of the 40 effective ablation sites leading to significant prolongation of the AF cycle length were judged retrospectively by CFAE maps as CFAE sites. Ablation at the sites exhibiting stable CFAE led to a significant AF cycle length prolongation also in 12 persistent AF patients (26).

In our long-standing persistent AF patients, the site of AF termination did not often directly correlate with the CFAE. However, most of the LA CFAE areas and more than half of CS CFAE areas had been targeted before achieving AF termination. In addition, in case of SR restoration from a residual localized AT source, 67 % of such sources correlated with one of the CFAE site on the preablation map. This finding supports the notion that localized AT sources unmasked by preceding extensive ablation display their activity as CFAE during AF before any ablation.

In conclusion, although limited ablation of the isolated AF driver may accidentally terminate persistent AF, this study in line with other observations suggests rather cumulative effect of successive ablation steps (including ablation of CFAE) on AF termination.

Limitations

Conventional electrogram-guided ablation in several patients may be considered a limitation of the study. This ablation step was employed to improve AF termination and outcome at the stage of significant AF organization after circumferential and linear ablation pointing to a suspect AF driver. On the other hand, this step terminated AF in only 9 (24 %) patients, and the successful ablation site was located within 20 mm of the closest CFAE site in only 4 of the patients.

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