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ORIGINAL RESEARCH

Severe and uniform bi-atrial remodeling measured by dominant frequency analysis in persistent atrial fibrillation unresponsive to ablation

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Abstract

Background High values of ECG and intracardiac dominant frequency (DF) are indicative of significant atrial remodeling in persistent atrial fibrillation (peAF). We hypothesized that patients with peAF unresponsive to ablation display higher ECG and intracardiac DFs than those remaining in sinus rhythm (SR) on the long term.

Methods Forty consecutive patients underwent stepwise ablation for peAF (sustained duration 19 ± 11 months). Electrograms were recorded before ablation at 13 left atrium (LA) sites and at the right atrial appendage (RAA) and coronary sinus (CS) synchronously to the ECG. DF was defined as the highest peak within the power spectrum.

Results peAF was terminated within the LA in 28 patients (left-terminated [LT]), whereas 12 patients remaining in AF after ablation (not left-terminated [NLT]) were cardioverted. Over a mean follow-up of 34 ± 14 months, all 12 NLT patients had a recurrence. Of the LT patients, 71% had a recurrence (20/28, LT_Rec), while 29% remained in SR throughout the follow-up (8/28, LT_SR). DF values and correlations between pairs of LA appendage (LAA), RAA, and CS DFs showed distinctive patterns among the subgroups. The NLT subgroup displayed the highest ECG and intracardiac DFs, with strong intragroup homogeneity between pairs of CS and LAA DFs, and to a lesser extent between pairs of CS and RAA DFs. Conversely, the LT_SR subgroup showed the lowest DFs, with significant intragroup heterogeneity between pairs of CS and both LAA and RAA DFs.

Conclusions Patients with peAF unresponsive to ablation show high surface and intracardiac DFs indicative of severe and uniform bi-atrial remodeling.

Keywords Atrial fibrillation · Catheter ablation · Dominant frequency · Intracardiac electrograms · Surface ECG · Electroanatomical remodeling

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1 Introduction

Progression of atrial fibrillation (AF) from acute to chronic form is accompanied by electrical and structural alterations of the atria, which provides diffuse substrate for AF perpetuation [1, 2] and compromises the success of persistent AF (peAF) ablation [3, 4]. Atrial signals extracted from surface ECG contain information about the dynamics of AF [5], with good correspondence between ECG and intracardiac electrogram (EGM) dominant frequencies (DFs) [6]. High values of ECG and EGM DF have been shown to be a marker for severe atrial electroanatomical remodeling (EAR) [7, 8] and independent predictors of AF recurrence after ablation [7, 9]. Our study is part of an ongoing project (REORGANIZE-AF) intended for measuring the level of AF disorganization in patients with peAF to predict restoration of sinus rhythm (SR) on the long term. We recently showed that patients with peAF unresponsive to catheter ablation had a higher level of baseline ECG disorganization than those with long-term maintenance of SR [10]. Herein, we report the baseline surface ECG and intracardiac DF distribution according to the long-term clinical outcome.

2 Methods

2.1 Electrophysiological study

More details are available in the Supplementary Material. The following catheters were introduced via the left and right femoral veins: a 3.5-mm cooled-tip catheter for mapping and ablation (Navistar Thermocool, Biosense Webster®), a circumferential duodecapolar Lasso® catheter (electrode spacing 2-6-2 mm, Biosense Webster®) within the left atrium (LA), a quadripolar catheter (electrode spacing 5-5-5 mm, 4 mm electrode tip size, Supreme, St. Jude Medical®) placed into the right atrial appendage (RAA), and a steerable decapolar catheter (electrode spacing 2-8-2 mm, 1 mm electrode tip size, Biosense Webster®) placed within the coronary sinus (CS), with the proximal electrode at the ostium. ECG chest lead V_6 was placed on the back (V_{6b}) of the patients, within the cardiac silhouette, in order to improve the recording of the LA activity [11, 12]. Sequential mapping of the LA was performed at baseline. The Lasso® catheter was consecutively placed in a stable position for 20 s at thirteen different LA locations: the ostium of the four pulmonary veins, the base of the left atrial appendage (LAA), the anterior and posterior parts of the roof, the middle and the inferior parts of the posterior wall, the mitral isthmus, and the superior, middle, and inferior parts of the septum. Synchronous to each LA site, 20-s EGMs were recorded within the RAA and CS simultaneous to the 12-lead ECG. Both ECG and EGMs were sampled at 2 kHz (Axiom Sensis XP®, Siemens®) for off-line analysis.

2.2 Ablation strategy

All patients underwent a stepwise catheter ablation (step-CA) procedure. The procedural endpoint was reached when AF was terminated in SR or atrial tachycardia (AT). When AF termination was not achieved, SR was restored by electrical cardioversion. Details of index and redo ablations are available in the Supplementary Material.

2.3 Study population

The study population consisted of 40 consecutive patients referred for a first ablation (mean age, 61 ± 8 years) suffering from AF for 6 ± 4 years, sustained for 19 ± 11 months before ablation and resistant to pharmacological or electrical cardioversion. The ablation procedures were performed by a single operator (EP) at the Lausanne University Hospital. Details of the clinical characteristics of the study population are provided in Table 1 and Supplementary Table S1. Clinical follow-up, including 48-h Holter recordings, was performed at scheduled visits at 3, 6, 12, 18, and 24 months, then every year. Recurrence was defined as AF or AT lasting more than 30 s [13]. This study has been performed in the framework of an ongoing project (REORGANIZE-AF) aimed at assessing the level of ECG and EGM organization in peAF in order to improve patients' selection for ablation. The study protocol was approved by the Human Research Ethics Committee of the Lausanne University Hospital, and all patients provided written informed consent.

Based on the procedural and clinical outcomes, the study population was divided into three subgroups: subgroup 1 (n = 8), patients in whom peAF was terminated into SR or AT by ablation within the LA who remained in SR throughout follow-up (left-terminated without recurrence, LT_SR); subgroup 2 (n = 20), patients in whom peAF was terminated by ablation within the LA who had a recurrence after a single step-CA procedure (left-terminated with recurrence, LT_Rec); and subgroup 3 (n = 12), patients in whom the step-CA procedure failed to terminate peAF within the LA (not left-terminated, NLT), all with recurrence at follow-up.

2.4 Intracardiac and ECG DF estimation

Digital signal processing was performed using MATLAB (The MathWorks Inc., Natick, MA, USA). All EGMs were visually checked and signals with noise or with ventricular far-field or recording artifacts were excluded from analysis. Signals were rectified and then bandpass filtered at 1–20 Hz [14]. Frequency spectra were estimated using the fast Fourier transform, and DF was identified as the highest peak frequency between 3 and 15 Hz. EGMs with a DF power (1-Hz band centered at the DF peak) lower than 20% of the total power in the 3–15-Hz band were reviewed to exclude spurious DF values [15, 16].

Table 1 Clinical characteristics of the study population

	All $n=40$	NLT 12 (30%)	LT_Rec 20 (50%)	LT_SR 8 (20%)	p value[1]	p value[2]	p value[3]
Age (years)	61 ± 8	62 ± 5	61 ± 10	60 ± 5	0.70	0.48	0.88
Sex (male/female)	38/2	12/0	18/2	8/0	0.51	0.99	0.99
AF duration (years)	6 ± 4	5 ± 3	6 ± 5	8 ± 3	0.4	*0.01*	0.23
Duration of sustained AF (months)	19 ± 11	26 ± 5	15 ± 6	17 ± 8	*0.01*	0.15	0.48
BMI (kg/m^2)	30 ± 6	29 ± 7	30 ± 7	28 ± 3	0.67	0.77	0.47
LVEF (%)	49 ± 11	53 ± 9	47 ± 12	51 ± 8	0.16	0.64	0.41
LA volume (ml)	170 ± 44	177 ± 41	167 ± 45	165 ± 46	0.51	0.55	0.9
Cumulative ablation time (min)	56 ± 19	72 ± 14	55 ± 12	38 ± 20	*0.001*	*0.001*	*0.01*

Values are mean ± SD or n (%). p-values < 0.05 are indicated in italic

AF atrial fibrillation, *BMI* body mass index, *LA* left atrium, *LT_Rec/LT_SR* left-terminated with/without recurrence at follow-up, *LVEF* left ventricular ejection fraction, *NLT* not left-terminated

[1] NLT vs. LT_Rec

[2] NLT vs. LT_SR

[3] LT_Rec vs. LT_SR

EGM DFs were computed on (1) the Lasso® catheter as the average DF of all dipoles, (2) the distal dipole from the RAA catheter, and (3) the five dipoles from the CS catheter. The surface DFs were computed on ECG leads V_1 to V_{6b} devoid of ventricular activity [10, 17]. More details are available in the Supplementary Material.

The DFs were first computed on 10-s epochs and then averaged over all available epochs for each patient. Hence, a single DF value was available for each catheter dipole and for each ECG lead per patient. For each patient, interatrial EGM and ECG left-to-right DF gradients were obtained as the difference between LAA and RAA DFs and between V_{6b} and V_1 DFs, respectively.

2.5 Statistical analysis

Continuous variables were expressed as mean ± SD. The differences between subgroups based on study outcomes were evaluated using the unpaired Student t test or Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Statistical significance was assumed for p values < 0.05. The correlation between ECG and EGM DF values according to study outcomes was estimated using Pearson's correlation coefficients. The homogeneity of the level of atrial remodeling according to study outcomes was evaluated using Pearson's correlation coefficients computed on pairs of DF values measured from LAA, RAA, and CS EGMs. The 95% confidence intervals (CI) for Pearson's correlation coefficients were obtained using bootstrap bias-corrected percentile method (1000 bootstrap replications) [18]. Correlation was considered significant at $p < 0.05$ if the 95% confidence interval did not include zero.

3 Results

3.1 Study population

peAF was terminated by ablation within the LA in 70% ($n = 28$, LT group) of the patients, whereas 30% ($n = 12$, NLT group) of the patients remained in AF at the end of the procedure and required electrical cardioversion to restore SR. AF termination occurred as ATs in 22 cases and as SR in 6 patients. Table 1 and Supplementary Table S1 report the baseline characteristics of the subgroups. After a single step-CA procedure, all 12 NLT patients and 20 LT patients (20/28, LT_Rec) had a recurrence, while 8 LT patients (8/28, LT_SR) remained in SR during follow-up. A gradual increase in ablation time was observed among the three subgroups, with the shortest in LT_SR patients, intermediate in LT_Rec patients, and longest in NLT patients (38 ± 20 vs. 55 ± 12 vs. 72 ± 14 min, $p < 0.01$). The NLT group also had significantly longer duration of sustained AF compared with the LT_Rec group (26 ± 5 vs. 15 ± 6 months, $p < 0.01$). Other clinical characteristics were similar between subgroups.

3.2 ECG and EGM DF values according to study outcomes

Figure 1 shows a representative example of DF estimation on 10-s epochs simultaneously acquired from ECG leads V_1 and V_{6b} and from the RAA and LAA in an LT_SR patient. For each ECG lead, the ECG is shown in blue and the atrial ECG devoid of ventricular activity in black. Note the similar values between atrial V_1 and RAA EGM DFs (5.27 Hz and 5.25 Hz, respectively) and between atrial V_{6b} and LAA EGM DFs (5.46 Hz and

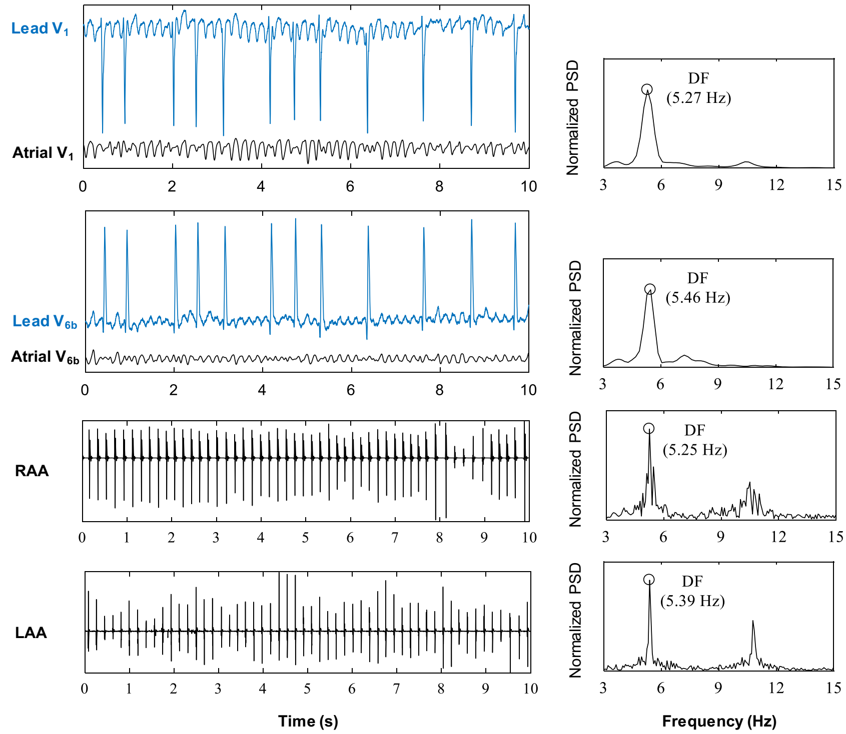

Fig. 1 Illustrative example of DF estimation on 10-s epochs simultaneously recorded from ECG leads V_1 and V_{6b} and from the RAA and LAA in an LT_SR patient. For each of the two ECG leads (the upper panels), the ECG signals before (blue) and after QRST cancelation (black) are illustrated. Synchronous 10-s intracardiac EGMs recorded from the RAA and LAA are displayed in the lower panels. The corresponding normalized power spectral densities and the estimated DFs are illustrated on the right side. DF, dominant frequency; ECG, surface electrocardiogram; EGM, intracardiac electrogram; LAA, left atrial appendage; LT_SR, left-terminated with no recurrence at follow-up; PSD, power spectral density; RAA, right atrial appendage

5.39 Hz, respectively). Figure 2 and Supplementary Tables S2 and S3 report the DF values computed on all ECG leads and EGMs for the entire study population and for the three subgroups. Significantly higher DFs were observed in the NLT subgroup compared with the two other subgroups for the RAA and mean LA (Fig. 2a) and for V_1 and V_{6b} (Fig. 2b). There was no significant difference in DF between the LT_Rec and LT_SR subgroups. Figure 2 c shows that the interatrial gradient of NLT patients was negative (− 0.40 ± 0.45 Hz) and significantly lower ($p < 0.05$) than that of LT_Rec and LT_SR patients in whom the gradient was positive (0.04 ± 0.34 Hz and 0.19 ± 0.58 Hz, respectively). Taken together, these findings suggest that patients without procedural termination and AF recurrence after a single step-CA display more advanced bi-atrial remodeling than patients in whom AF was terminated within the LA without recurrence.

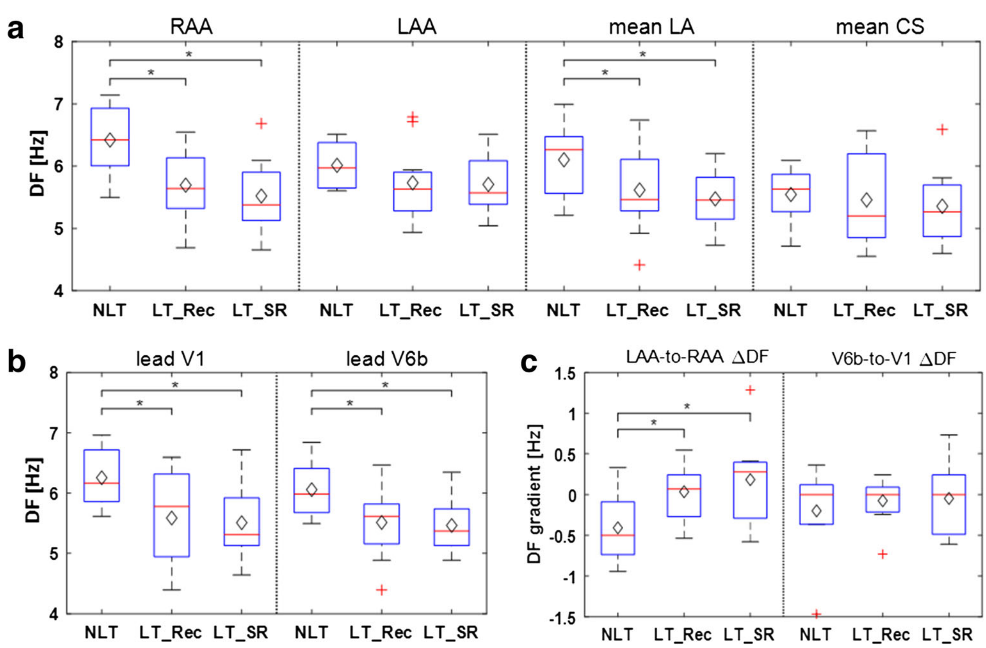

Fig. 2 ECG and EGM DF values for the NLT, LT_Rec, and LT_SR subgroups. **a** RAA DFs, LAA DFs, mean LA DFs (13 LA sites), and mean CS DFs (5 CS dipoles). **b** ECG V_1 and V_{6b} DFs. **c** Interatrial LAA-to-RAA and surface V_1-to-V_{6b} DF gradients. *$p < 0.05$; CS, coronary sinus; LA, left atrium; LT_Rec, left-terminated patients with recurrence at follow-up; ΔDF, dominant frequency gradient; other abbreviations as in Fig. 1

Table 2 Correlation coefficients between ECG and EGM DFs

	V_1	V_2	V_3	V_4	V_5	V_{6b}	RAA	LAA
V_1	–	*0.72* [0.51, 0.88]	*0.60* [0.31, 0.80]	*0.68* [0.52, 0.79]	0.28 [− 0.01, 0.56]	*0.72* [0.53, 0.84]	*0.90* [0.75, 0.98]	*0.62* [0.37, 0.76]
V_{6b}	*0.72* [0.53, 0.84]	0.25 [− 0.03, 0.51]	0.15 [− 0.18, 0.46]	*0.47* [0.14, 0.68]	*0.49* [0.19, 0.73]	–	*0.72* [0.53, 0.83]	*0.83* [0.70, 0.94]
$CS_{1–2}$	*0.51* [0.15, 0.76]	0.16 [− 0.22, 0.45]	0.21 [− 0.23, 0.53]	0.26 [− 0.20, 0.60]	*0.39* [0.09, 0.58]	*0.69* [0.51, 0.82]	*0.67* [0.42, 0.81]	*0.74* [0.42, 0.88]
$CS_{9–10}$	*0.59* [0.31, 0.77]	*0.41* [0.12, 0.67]	*0.40* [0.08, 0.68]	*0.35* [0.05, 0.61]	0.06 [− 0.22, 0.42]	*0.65* [0.44, 0.83]	*0.63* [0.36, 0.81]	*0.68* [0.38, 0.84]
RAA								*0.79* [0.58, 0.90]
ECG V_{6b}-to-V_1 DF gradient vs. interatrial left-to-right DF gradient *0.63* [0.26, 0.84]								

Correlation coefficients significant at $p < 0.05$ (95% CI does not include the value 0) are indicated in italic. 95% bootstrap bias-corrected CI are shown in brackets

CI confidence intervals, *CS* coronary sinus, *DF* dominant frequency, *ECG* surface electrocardiogram, *EGM* intracardiac electrogram, *LAA* left atrial appendage, *RAA* right atrial appendage

3.3 Correlation between ECG and EGM DF values according to study outcomes

Table 2, Supplementary Table S4, and Fig. 3 show the correlation coefficients between the DF values estimated from ECG leads V_1 to V_{6b} and those estimated from LAA, RAA, and CS EGMs for the entire study population. The RAA DF (solid blue line) had the highest correlation with V_1 ($r = 0.90$, 95% CI [0.75, 0.98], $p < 0.001$), which progressively dropped until V_5 ($r = 0.27$, 95% CI [− 0.01, 0.54], $p =$ ns), then increased for V_{6b} ($r = 0.72$, 95% CI [0.53, 0.83], $p < 0.001$). The LAA DF (solid green line) showed the opposite pattern with the highest correlation with V_{6b} ($r = 0.83$, 95% CI [0.70, 0.94], $p < 0.001$) and a moderate correlation with V_1 ($r = 0.62$, 95% CI [0.37, 0.76], $p < 0.001$). Linear regression analysis shows in Supplementary Figure S2 that ECG V_1 and V_{6b} DFs were significantly correlated with RAA and LAA DFs, respectively, and that both appendages were significantly correlated as well. High and significant correlations were also found between RAA and V_1 DFs ($r > 0.86$, $p < 0.001$) and between LAA and V_{6b} DFs ($r > 0.78$, $p < 0.01$) in each subgroup (Table 3), suggesting that V_1 and V_{6b} DFs are acceptable surrogates for RAA and LAA DFs, respectively, independent of study outcomes.

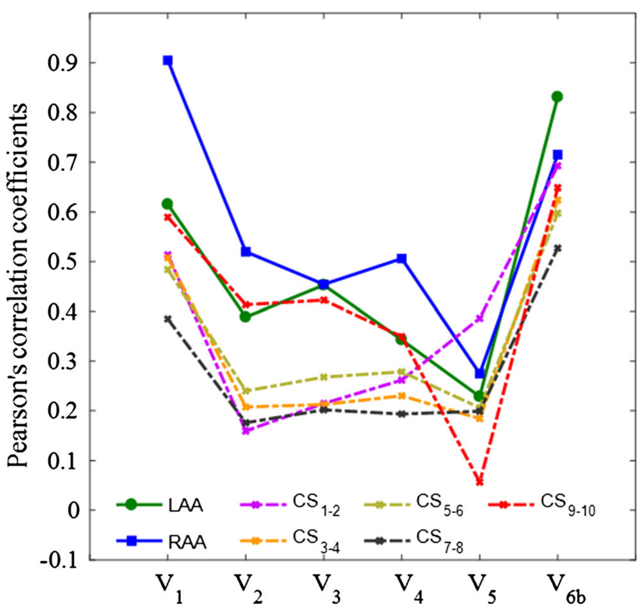

Fig. 3 Pearson's correlation coefficients between ECG leads and the LAA (solid green line), RAA (solid blue line), and CS (dashed lines) EGMs for the entire study population. Abbreviations as in Figs. 1 and 2

Figure 3 shows for the entire study population that each CS dipole (dashed lines) displayed a correlation pattern with ECG leads similar to that of LAA and RAA EGMs but of lower magnitudes. Overall, the CS DFs were best correlated with the DFs of leads V_1 and V_{6b} and were largely uncorrelated with leads V_2 to V_5. Table 2 and Supplementary Table S4 also report the correlation between pairs of ECG leads, which tended to decrease with increasing distance between leads except for V_{6b} and V_1, which were highly correlated ($r = 0.72$, 95% CI [0.53, 0.84], $p < 0.001$). Similar results were found for each subgroup (Supplementary Table S5). Altogether, these findings show that leads V_1 and V_{6b} DFs reflect the DFs of the RAA and LAA, and to a lower extent the CS DFs, while the remaining chest leads had weaker correlation with these structures.

3.4 Homogeneity of the EAR level within subgroups according to study outcomes

The homogeneity of the level of bi-atrial and CS EAR within each subgroup was assessed by measuring the interindividual variability of pairs of DF values from the LAA, RAA, and CS EGMs using Pearson's correlation (Table 3 and Supplementary Table S5).

Table 3 Correlation coefficients between ECG and EGM DFs within subgroups according to study outcomes

		V_{6b}	RAA	LAA
V_1	NLT	0.34 [− 0.35, 0.89]	*0.89* [0.65, 0.99]	0.32 [− 0.31, 0.79]
	LT_Rec	*0.69* [0.21, 0.90]	*0.86* [0.41, 0.89]	*0.66* [0.36, 0.85]
	LT_SR	*0.82* [0.17, 0.98]	*0.97* [0.86, 0.99]	0.49 [− 0.64, 0.98]
V_{6b}	NLT		*0.57* [0.12, 0.92]	*0.79* [0.27, 0.93]
	LT_Rec		*0.62* [0.25, 0.81]	*0.78* [0.22, 0.98]
	LT_SR		0.74 [− 0.11, 0.96]	*0.94* [0.71, 0.99]
$CS_{1–2}$	NLT		0.39 [− 0.09, 0.75]	*0.83* [0.57, 0.95]
	LT_Rec		*0.74* [0.45, 0.89]	*0.63* [0.04, 0.96]
	LT_SR		0.46 [− 0.88, 0.99]	0.77 [− 0.50, 0.99]
$CS_{9–10}$	NLT		0.42 [− 0.67, 0.85]	*0.92* [0.49, 0.98]
	LT_Rec		0.42 [− 0.09, 0.76]	*0.60* [0.21, 0.85]
	LT_SR		0.52 [− 0.10, 0.97]	0.52 [− 0.61, 0.96]
RAA	NLT			*0.79* [0.29, 0.93]
	LT_Rec			*0.80* [0.53, 0.92]
	LT_SR			0.50 [− 0.63, 0.94]
ECG V_{6b}-to-V_1 DF gradient vs. interatrial left-to-right DF gradient				
NLT 0.50 [− 0.32, 0.90]				
LT_Rec 0.38 [− 0.07, 0.67]				
LT_SR *0.95* [0.82, 0.99]				

Correlation coefficients significant at $p < 0.05$ (95% CI does not include the value 0) are indicated in italic. 95% bootstrap bias-corrected CI are shown in square brackets

LT_Rec/LT_SR left-terminated with/without recurrence at follow-up, *NLT* not left-terminated; other abbreviations as in Table 2

Table 3 shows that LAA and RAA DF values were significantly correlated in the NLT and LT_Rec subgroups ($r > 0.79$, $p < 0.01$), but not in the LT_SR subgroup ($r = 0.5$, $p =$ ns). In contrast, the interatrial left-to-right DF and the ECG V_{6b}-to-V_1 DF gradients were only correlated in the LT_SR subgroup. The three subgroups displayed divergent patterns of correlations between CS dipoles and LAA and RAA DFs (Fig. 4). Figure 4 a shows that NLT patients had a strong intragroup homogeneity between pairs of all CS dipoles and LAA DFs ($r > 0.76$, $p < 0.05$) and some intragroup heterogeneity between pairs of CS dipoles and RAA DFs ($r < 0.64$, $p =$ ns). Figure 4 b shows that LT_SR patients displayed a strong intragroup heterogeneity between pairs of CS dipoles and both LAA and RAA DFs ($p =$ ns). Figure 4 c shows an intermediate pattern with moderate correlations between CS and both LAA and RAA DFs ($r \approx 0.60$, $p < 0.05$) for the LT_Rec subgroup. In conclusion, NLT patients, all with recurrences at follow-up, displayed as a group the strongest homogeneity between pairs of LAA and CS DF values and between pairs of LAA and RAA DF values, suggestive of uniform bi-atrial remodeling.

4 Discussion

4.1 Main findings

This study contains several findings summarized as follows: (1) peAF not terminated by ablation within the LA displayed as a group severe and homogenous bi-atrial EAR, as shown by high bi-atrial and CS DF values, a negative left-to-right DF gradient, and 100% recurrence rate at follow-up; (2) conversely, peAF terminated within the LA without recurrence at follow-up had a short ablation time, low bi-atrial DF values, and a positive interatrial left-to-right DF gradient suggestive of less advanced EAR; and (3) right and left appendage DFs can be noninvasively estimated using ECG leads V_1 and V_{6b}, respectively.

4.2 Correlation between ECG and intracardiac EGM DFs in patients with peAF

Several studies using standard ECG lead configuration or body surface potential mapping (BSPM) reported a good concordance between ECG and intracardiac EGMs in patients with AF [6, 11, 12, 19]. The RA activity during AF appears as a major contributor to the f-waves recorded from lead V_1 [6, 12, 19] while posterior leads best reflect the LA activity [11]. Our study confirms these previous findings by showing a high correlation between RAA and lead V_1 DFs and to a lesser extent between LAA and lead V_{6b} DFs.

We also investigated the cross-correlation between ECG chest leads. The best correlation was found between nearby ECG leads and dropped with interelectrode distance, except for leads V_1 and V_{6b}. The high correlation between these two distant leads appears related to their strong correlation with the RAA and LAA, both largely correlated as well, and to their location on the axis crossing the right and left atria. Based on the solid angle theory [20], any leads in-between V_1 and V_{6b} will represent an intermingled contribution of both atrial activities. These findings are in line with a strong side-specific

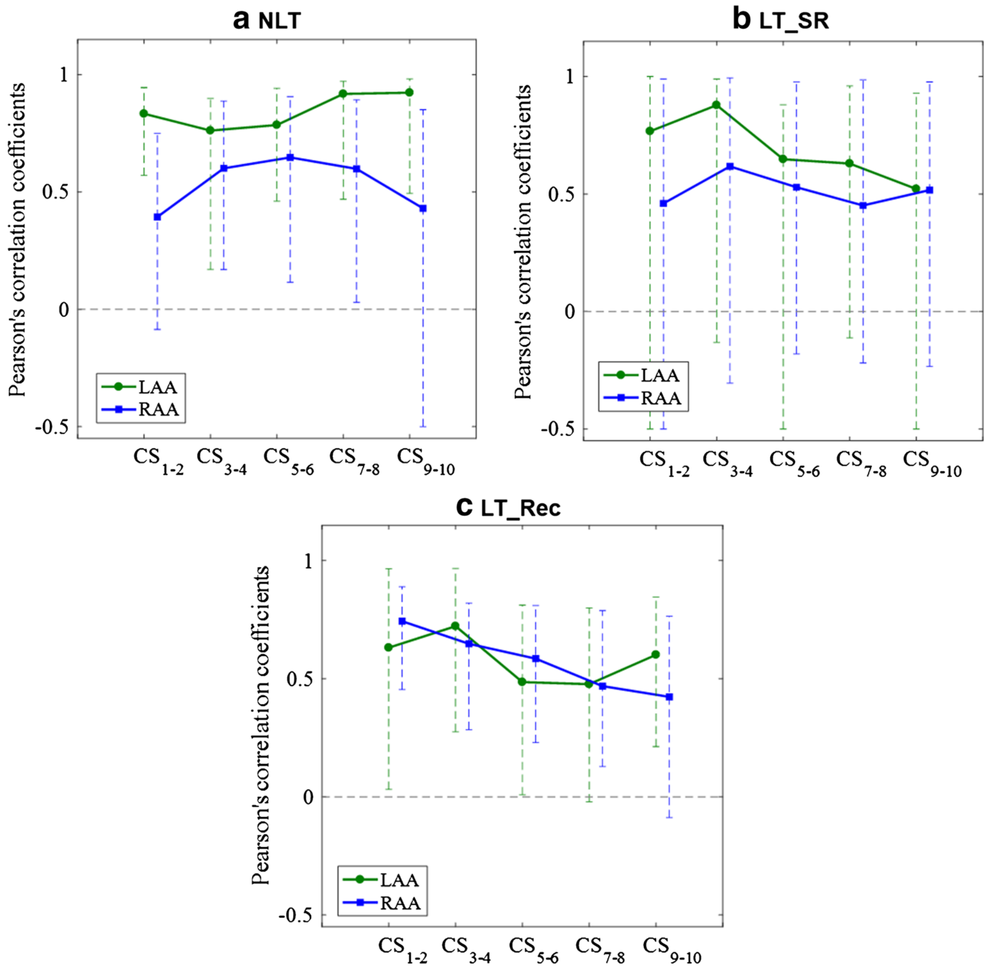

Fig. 4 Pearson's correlation coefficients between CS dipoles and LAA (green line with circle markers) and RAA (blue line with square markers) according to study outcomes. **a** NLT subgroup. **b** LT_SR subgroup. **c** LT_Rec subgroup. The vertical dashed lines indicate the 95% bootstrap bias-corrected CI (1000 bootstrap replications). Correlations were significant at $p < 0.05$ if the 95% CI did not include zero. CI, confidence interval; other abbreviations as in Figs. 1 and 2

correspondence between surface and intracardiac frequency activity as reported by Guillem et al. using BSPM [12].

Conflicting results were reported regarding the correlation between CS activity and surface ECG. Uetake et al. [6] showed a good correlation between the CS and all ECG lead DFs, while others found a correlation only with V_1 [7, 21]. Our results show a complex pattern of correlation between CS and ECG lead DFs with a "U-shaped" curve from V_1 towards V_{6b}. In addition, ECG leads displayed lower correlation values with the CS dipoles than with the RAA and LAA. The CS is considered as the 5th cardiac structure because of its circumferential striated muscle [22]. Taken together, our results suggest that CS EGMs include some local activity [22] mixed up with contributions from both atria.

4.3 Bi-atrial EAR level according to study outcomes

The temporal evolution of AF from acute to chronic stages is accompanied by several electroanatomical alterations of the atria [1], which makes the success of peAF ablation suboptimal [4]. A better characterization of AF substrate may help identify patients with peAF unresponsive to ablation. The DECAAF study has recently shown that the extent of left atrial tissue fibrosis estimated by delayed enhancement magnetic resonance imaging is an independent predictor of the AF recurrence after ablation [23]. Moreover, intracardiac DF is a surrogate of atrial remodeling, with high DF values indicative of advanced remodeling [1, 7, 8]. In our study, patients in whom AF was not terminated by ablation within the LA (NLT subgroup), all with recurrence at follow-up, systematically displayed higher intracardiac and ECG DF values than patients in whom AF was terminated. Moreover, the NLT subgroup had a negative interatrial left-to-right DF gradient poorly correlated with the ECG V_{6b}-to-V_1 DF gradient, which is suggestive of severe RA remodeling and a high number of bi-atrial drivers [24]. In contrast, the LT_SR subgroup displayed a positive interatrial left-to-right DF gradient highly correlated with the ECG V_{6b}-to-V_1 DF gradient, suggesting that the surface ECG closely reflects the atrial activity of the two appendages, which fits with mild bi-atrial EAR and AF drivers mainly located within the LA [24]. Altogether, these findings are in line with previous papers showing high and rather homogeneous bi-atrial DF values [25] and advanced bi-atrial remodeling [26] in peAF.

4.4 Homogeneity of the EAR level according to study outcomes

To the best of our knowledge, this is the first study assessing the homogeneity of the bi-atrial EAR level within subgroups of peAF patients according to ablation and follow-up outcomes. Our study showed that NLT patients displayed as a group a strong interpatient homogeneity between pairs of LAA and CS DFs, and LAA and RAA DFs, and to a lesser extent between pairs of CS and RAA DF values. This high and homogeneous remodeling affecting all atrial cavities fits with experimental models showing an increasing complexity and stability of the AF substrate with longer peAF duration such as endo-epicardial dissociation and dyssynchronous activities [27]. High DF values and the strong correlation between pairs of CS and LAA DFs are indicative of uniform CS and LA remodeling [25]. Some studies recently suggested a role played by the CS in sustaining AF [28, 29]. High DFs at the proximal CS were found to be correlated with procedural outcomes [28], while others found that CS disconnection from the LA lowered the probability of inducible sustained AF [29]. Whether a systematic ablation of the CS should be undertaken to restore SR in patients with severe and uniform bi-atrial EAR was not part of our study design and needs to be further investigated.

The LT_SR subgroup, who remained in SR during follow-up after a single procedure, showed an opposite pattern of correlations between pairs of LAA, RAA, and CS DFs compared with the NLT subgroup. LT_SR patients displayed as a subgroup a high variability between pairs of CS dipoles and both LAA and RAA DFs. Moreover, these patients had short ablation time until AF termination, low ECG and intracardiac DF values, and positive interatrial left-to-right DF gradient, all indicative of a low level of AF complexity [24, 25]. Altogether, these findings indicate that the subgroup of patients with a successful ablation displays lower bi-atrial and CS remodeling and higher interindividual heterogeneity of the remodeling level than that of the patients with peAF unresponsive to ablation.

4.5 Limitations

First, this study is limited by the small size of the population, which might minimize the confidence of the results due to lack of power. However, patients were consecutively included and the analysis was performed after the step-CA procedure, preventing any selection bias. Second, the short duration (20 s) of the synchronous ECG and EGM recordings precluded any measurement of LAA, RAA, and CS DF coupling. Further study is needed to evaluate whether the strength of DF coupling is predictive of ablation outcomes. Third, the clinical endpoint was defined as a successful ablation after a single procedure, which might minimize the success rate of step-CA after multiple procedures [10]. Importantly, our study is designed to identify (before any ablation) ECG- and EGM-based markers to characterize the AF substrate in relation with procedural and clinical outcomes. Since most of the recurrences were ATs, using single ablation success as a clinical endpoint was aimed at lowering the bias due to repeat ablation procedures. High recurrence rate as ATs may be a consequence of the extensive ablation following the index procedure which included pulmonary vein isolation, defragmentation, and lines. Any gap in these lesions may favor the emergence of ATs. Importantly, the recurrence appearing as ATs may be both the expression of the ablation extent and the level of bi-atrial remodeling [30]. Finally, for the patients in whom AF was not terminated during ablation, the procedure was ended when no more fragmented EGMs could be found based on the operator's appreciation. This decision might subjectively affect the procedural duration, and any assumptions regarding a causal relationship between the level of AF disorganization and ablation time should be taken with caution.

5 Conclusions

This study shows that patients with peAF unresponsive to ablation, all with recurrences at follow-up, displayed as a group advanced bi-atrial and CS remodeling as indicated by high ECG and intracardiac DF values. Conversely, peAF terminated during ablation without recurrence at follow-up after a single procedure displayed as a group mild bi-atrial and CS remodeling. These findings suggest that remodeling level measured by DF analysis may help identify patients with peAF unresponsive to ablation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study protocol was approved by the local ethics committee of the Lausanne University Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

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