A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left?

Short Title

Bi-atrial substrate correlation in persistent AF.

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Abstract

Introduction:

The right atrium (RA) is readily accessible; however, it is unclear whether changes in the RA are representative of the LA. We performed detailed bi-atrial electroanatomic mapping to determine the electrophysiological relationship between the atria.

Methods and Results

Consecutive patients with persistent AF underwent bi-atrial electroanatomical mapping with a contact force catheter acquiring points with a CF >10g prior to ablation. Points were analyzed for tissue voltage, complex electrograms, low voltage (<0.5mV), scar (<0.05mV) and conduction velocity (CV). Forty patients (mean age 59 ± 9.2 yrs, AF duration 12.9 ± 9.2 months, LA area: 28 ± 5.2 , RA area: 25 ± 6.4 mm², LVEF: $44 \pm 15\%$) underwent mapping during CS pacing. Bipolar voltage ($R=0.57$, $p<0.001$), unipolar voltage ($R=0.68$, $p<0.001$), low voltage (<0.5nV) ($R=0.48$, $p=0.002$), fractionation ($R=0.73$, $p<0.001$) and CV ($R=0.49$, $p=0.001$) correlated well between atria. There was no difference in global bipolar voltage (LA 1.89 ± 0.77 vs RA 1.77 ± 0.57 mV, $p=0.57$); complex electrograms (LA 20% vs RA 20%, $p=0.99$) or low voltage (LA 15% vs RA 16%, $p=0.84$). Global unipolar voltage was significantly higher in the LA compared the RA (2.95 ± 1.14 vs 2.28 ± 0.65 mV, $p=0.002$) and CV was significantly slower in the RA compared to the LA (0.93 ± 0.15 ms⁻¹ vs 1.01 ± 0.19 ms⁻¹, $p=0.001$).

Conclusion

AF is associated with remodeling processes affecting both atria. The more accessible RA provides an insight into the bi-atrial process associated with AF in various disease states without transseptal access.

Keywords

Bi-atrial

Substrate

Atrial Fibrillation

Remodelling

Introduction

The atrial substrate, beyond the pulmonary veins, is fundamental to the maintenance and progression of paroxysmal to persistent atrial fibrillation^{1,2}. Atrial fibrillation is associated with a range of conditions such as ageing, hypertension, obesity, heart failure and sleep apnea which may be expected to produce bi-atrial changes and are associated with an increase in AF following catheter ablation^{3-6,7}. In clinical research, electroanatomic mapping of the right atrium can be safely performed without exposing patients to transseptal puncture without the justification of a clinical requirement. As such many studies^{3-6,8} exploring the atrial substrate associated with the risk factors for AF have been confined to the right atrium as a surrogate for the remodelling process in the left atrium. There are obvious structural differences between the two chambers with the vena cavae and the crista terminalis unique to the RA and the pulmonary veins a feature of the LA. However, much of the atria is common to both including the body, the appendages and perivalvular tissue. Although bi-atrial mapping has been extensively performed, a detailed correlation of the electrical and structural remodelling processes between the atria has not been completed^{3,9}. The aim of the present study was to determine if electrical and structural changes in the right atrium are truly representative of the left atrium.

Methods

Study population

Consecutive patients undergoing index AF ablation were prospectively enrolled across 2 centers. Patients were included if they had persistent AF of at least 3 months continuous duration and were in AF at time of ablation, as this burden of AF was expected to be associated with significant electrophysiologic and electroanatomic change. Patients were excluded if they (1) had paroxysmal AF; (2) were unable to be electrically cardioverted to sinus rhythm; or (3) had active or uncontrolled thyroid disease; (4) had undergone previous left atrial ablation; or (5) were unable or unwilling to consent. The study was approved by the human research and ethics committee at both of the centers involved in the study.

Mapping Technique

Peri-procedural management

Antiarrhythmic medications were discontinued five half lives prior to procedure. Anticoagulation was ceased 2 days prior to ablation or continued (in the case of vitamin K antagonists) at operator discretion. Following trans-esophageal echocardiography to exclude intra-cardiac thrombus, double transseptal access was performed and intravenous heparin administered to a target ACT >350s.

Electro-anatomical mapping

Left atrial geometry was constructed using a 20 pole lasso catheter (Biosense Webster Inc, CA, USA) and registered with the pre-procedural CT or MRI using CARTO3 electro-anatomical mapping system. Electrical cardioversion to sinus rhythm was then performed. Mapping was performed with a 4mm irrigated smart-touch ablation catheter (Biosense Webster Inc, CA, USA) with contact force capability prior to ablation during pacing from the coronary sinus at 600ms. At least 150 points across all atrial regions, up to but not including the pulmonary vein (PV), ostia were collected with the assistance of the Confidense™ module (Biosense Webster Inc, CA, USA) to ensure an even point distribution. Only points with contact force >10g were included for analysis. Mapping was performed in an identical fashion in the right atrium following left atrial ablation, but prior to any right atrial ablation such as a cavotricuspid isthmus ablation.

Electrogram Analysis

Electrogram analysis was performed offline post procedure. Points were analyzed at 200mm/s sweep speed for complex fractionated electrograms (CFE), low voltage and scar. Complex fractionated electrograms (CFE) were defined as electrograms with ≥ 3 deflections *and* ≥ 50 ms duration. Percentages represent the proportion of total points across the entire atria for global analysis or within each region according to the defined criteria for CFE, low voltage or scar. Global and regional voltage (unipolar and bipolar) was determined by the average voltage across the entire atria for global analysis or within each region for regional analysis. For the purposes of regional analysis, the atria were divided into four discrete segments (see figure 1).

Tissue Voltage

Unipolar and bipolar voltage was recorded for each point as the maximum voltage difference between the highest and lowest amplitude deflections. Points with bipolar voltage $\leq 0.5\text{mV}$ were defined as low voltage.

Conduction velocity

Conduction velocity (CV) was determined using methodology previously described⁵. In brief, five pairs of points were selected in areas of least isochronal crowding in each of 4 regions to obtain a global conduction velocity. Conduction was measured perpendicular to isochrones, at five isochronal steps. CV was determined by dividing the measured shortest surface distance between point pairs by the difference in local activation time. Regional CV was determined as the average CV measured from five different point pairs in each region. Global CV consisted of the average of each regional CV within each atrium.

Statistical analysis

Based on previous studies correlating bi-atrial volume as detected on CT in the setting of AF (as a surrogate for atrial remodeling), an expected R value of 0.51 was determined^{10, 11}. For a statistical power of 80%, and two-tailed α value of 0.05, a sample size of 28 was calculated. Data are expressed as mean $\pm$ standard deviation (SD) unless otherwise indicated. After assessment of normal distribution with the Kolmogorov–Smirnov test, two-group comparisons were made using Student's t test for continuous variables, or the Chi-squared test for categorical variables. The independent samples Mann-Whitney U test was used for non-normally distributed variables. Co-efficient of variation was determined by the mean divided by the standard deviation. Correlation was determined by Pearson's correlation co-efficient. A two-tailed p value

of <0.05 was considered significant. Analyses were conducted using SPSS software (version 23, IBM, Chicago, Illinois).

Results

Study Population (Table 1)

Forty patients undergoing AF ablation underwent biatrial mapping. The baseline characteristics of the patients are outlined in Table 1. The population was predominately male (90%) with a mean age of 59 ± 9.2 years, CHADS₂ score of 1.1 ± 0.8 , and a BMI of 29.1 ± 4.2 kg/m². Persistent AF was longstanding in 67.5% with an average duration of continuous AF of 12.9 ± 9.2 months and 85% of patients had undergone previous electrical cardioversion.

Electro-anatomical Mapping (Table 2, Figure 2)

The mean number of points was 220 ± 66 points in the LA and 216 ± 54 points in the RA with no difference between the atria ($p=0.76$).

Global Tissue Voltage (Figure 2A)

There was a significant correlation in global bipolar voltage between the left and right atria ($R=0.57$, $p<0.001$). There was no significant difference in global bipolar voltage between the left and right atria (1.89 ± 0.77 vs 1.77 ± 0.57 mV, $p=0.45$) There was a strong correlation in global unipolar voltage between the left and right atria ($R=0.68$, $p<0.001$). Unipolar voltage was significantly higher in LA compared to the RA (2.95 ± 1.14 vs 2.28 ± 0.65 mV, $p<0.002$). Within

each atrium, there was a very strong correlation between global bipolar and unipolar tissue voltages (LA: $R=0.94$, RA: $R=0.95$, $p<0.001$ for each).

No significant regional variation in bipolar voltage was noted with the exception of the posterior segment, which was significantly lower in the RA compared to the LA (1.18 ± 0.48 in RA vs 1.77 ± 0.77 mV, $p<0.001$). Compared to the LA, unipolar voltage in the RA was significantly lower in the posterior (1.56 ± 0.54 vs 2.92 ± 1.22 mV, $p<0.001$) and lateral areas (2.36 ± 0.84 vs 3.24 ± 1.30 mV, $p<0.001$) in the region of the crista terminalis. Bi-atrial bipolar and unipolar tissue voltage correlated well regionally (Table 3).

Low Voltage

The mean number of points in each atrial detecting low voltage or scar was 34 ± 23 points in the RA and 42 ± 44 points in the LA. There was a significant correlation in the proportion of low voltage (<0.5 mV) between the RA and LA ($R=0.48$, $p=0.002$). There was no significant difference in the percentage of low voltage (<0.5 mV) between the RA ($15.7 \pm 10.3\%$) and LA ($15.0 \pm 15.7\%$, $p=0.84$). Low voltage regions were present in the LA in 88%, the RA in 98% and bi-atrially in 95% of patients. Scar regions (bipolar voltage <0.05 mV) were present in the LA in 45%, in the RA in 28% and bi-atrially in 20% of patients (Table 2).

Complex Fractionated Electrograms (CFE's)

There was a strong correlation in the presence of CFE's between the RA and LA ($R=0.73$, $p<0.001$). There was no significant difference in the proportion of CFEs ($20.0 \pm 14.2\%$ in the RA

vs $20.0 \pm 15.2\%$ in the LA, $p=0.73$). Within regions of low voltage or scar fractionation was present in the LA in $8.7 \pm 9.8\%$ and RA in $8.0 \pm 7.8\%$, $p=0.73$), which correlated significantly ($R=0.53$, $p<0.001$). Fractionation made up $40 \pm 29\%$ of low voltage or scar points in the RA and $44 \pm 35\%$ in LA ($p=0.5$), with no significant correlation between chambers($R=0.30$, $p=0.061$).

Conduction Velocity (Table 2)

There was a significant correlation in global conduction velocity (CV) between the RA and LA ($R=0.49$, $p=0.001$, Figure 2B). CV correlated well regionally, with the exception of the septal region (Table 3). Global conduction velocity (CV) was notably slower in the RA compared to the LA ($0.93 \pm 0.15\text{ms}^{-1}$ vs $1.01 \pm 0.19\text{ms}^{-1}$, $p=0.02$).

Discussion

We performed detailed high density electro-anatomical mapping using contact force in 40 patients with persistent AF undergoing AF ablation in order to compare the atrial substrate between the left and right atria. Although bi-atrial mapping has been previously performed, direct comparisons between atria have not been determined. In the present study there was a significant correlation between right and left atrium in:

1. Global unipolar and bipolar voltage;
2. Low voltage, scar and the presence of complex fractionated activity;
3. Global conduction velocity although conduction was significantly slower in the RA compared the LA.

To our knowledge, this is the first study to directly compare the atrial substrate between the left and right atria in a cohort of patients with persistent AF. Furthermore, our study is the first to undertake bi-atrial electroanatomical mapping with the aid of contact force sensing technology, allowing a true differentiation of electrogram morphology from electrograms that may be explained by poor tissue contact. This provides a more accurate characterization of the atrial substrate particular in regions of low voltage¹².

Does the right atrium represent the left?

A better understanding of the human atrial substrate in atrial fibrillation is the cornerstone in improving pharmacologic and ablation based strategies in persistent AF. Prior studies have provided a detailed characterisation of the electrical and structural changes in the right atrium alone in various disease states including hypertension^{5,6}, ageing⁸, heart failure⁴, mitral valve disease³, as well as paroxysmal and persistent AF^{7,13}. Right atrial mapping is attractive in the research setting as access is generally uncomplicated, safer and avoids the need for transseptal access with its incumbent risks and ethical questionability in the setting of a purely non-clinical intervention. One may postulate that remodelling observed in the right atrium is an accurate representation of the left; however, to our knowledge, this has not been specifically addressed. We sought to evaluate, whether such inferences maybe validly drawn.

Tissue Voltage and Fractionation

Although left atrial remodelling in the setting of persistent AF have been well described, few reports have performed bi-atrial mapping. Stiles et al performed bi-atrial mapping in no or low burden ('lone') AF (n=25) and demonstrated lower bipolar voltage, an increase in fractionation,

with changes in AF comparable between the LA and RA (RA: $1.7 \pm 0.4\text{mV}$, LA: $1.7 \pm 0.7\text{mV}$)⁹. John et al performed bi-atrial substrate analysis in rheumatic mitral disease and also demonstrated comparable voltages between the RA and LA³. Sanders et al performed RA substrate analysis in patients with LV dysfunction (in effect a bi-atrial remodeling factor) and noted electrophysiological changes mirroring those seen in high burden AF, including the presence of RA scar in 75% of patients with heart failure⁴.

Remodelling is not confined to the left atrium which is not surprising given AF involves both atria and many of the associated disease states such as heart failure⁴, aging⁸, valvular disease³ and hypertension⁶, stimulate neurohormonal pathways with systemic sequelae. These processes, which include AF itself^{14, 15}, atrial stretch^{3, 16}, inflammation¹⁷, oxidative stress¹⁸, autonomic neural activity^{19, 20} and the activation of the renin-angiotensin system^{21, 22} and sympathetic nervous system have been well described in human and animal models. Figure 3 illustrates the interplay of these processes in bi-atrial structural remodelling.

In the present study bi-atrial mapping was performed during paced rhythm as electrophysiological parameters are more reliable and reproducible compared with assessment during AF. Atrial voltage is significantly lower when measured in AF. Furthermore, regions of CFE and low voltage apparent in AF frequently correlate with regions of normal conduction, electrogram morphology and voltage when reassessed in paced rhythm^{12, 23-25}. The outcomes for catheter ablation for AF may also be improved when performed in sinus rhythm. Kochhäuser et al reported that the presence of sinus rhythm early during catheter ablation for persistent AF predicted greater freedom from AF at 18 months follow up. The authors hypothesized that improved signal voltage in sinus rhythm improved ablation endpoints²⁶.

In the present study, there was a significant correlation in complex fractionated activity ($R=0.73$, $p<0.001$), tissue voltage (Bipolar: $R=0.57$, $p<0.001$, Unipolar: $R=0.68$, $p<0.001$) and low voltage ($R=0.55$, $p=0.002$) between the RA and LA. These findings suggest that prior studies confined to the RA offer important insights and are an accurate representation of the left atrial substrate.

Conduction Velocity

To our knowledge, this study is the first to provide a direct comparison between the atria and demonstrate a significant reduction in conduction velocity in the RA relative to the LA in persistent AF. Although there was an absolute difference in CV between atria, a significant correlation remained both globally and regionally aside from the septum. There are important electroanatomic differences between the atria, which may in part explain this observation. In the right atrium there is the complex region of the crista terminalis which incorporates the sinus node complex and the junction of the smooth and trabeculated right atrium²⁷. In contrast, the left atrial endocardium houses the pulmonary veins, surrounding antrum and septopulmonary bundle; hence, differences in the posterior atria may be expected considering inherent anatomic differences. Slowing of right atrial conduction in the AF population is well recognized in the clinical coupling of sick sinus syndrome and atrial fibrillation²⁸. Conduction slowing in the RA relative to the LA may in part be explained by stretch mediated effects particularly at the vulnerable junction of the smooth and trabeculated region of the crista terminalis¹³. Despite anatomical differences between the atria there was a significant correlation between the atria, which may be attributable to systemic or neurohormonal mechanisms rather than local factors.

Mechanisms Responsible for Bi-atrial Structural Remodeling (Figure 3)

Although rapid firing from the pulmonary veins is the major source of triggers for AF²⁹ the atrial substrate becomes increasingly important in the maintenance of persistent AF³⁰. Remodelling is not confined to the left atrium, which is not surprising given AF involves both atria and many of the associated disease states such as heart failure⁴, aging⁸, valvular disease³ and hypertension⁶, stimulate neurohormonal pathways with systemic sequelae. These processes, which include AF itself^{14, 15}, atrial stretch^{3, 16}, inflammation¹⁷, oxidative stress¹⁸, autonomic neural activity^{19, 20} and the activation of the renin-angiotensin system^{21, 22} and sympathetic nervous system have been well described in human and animal models. Figure 3 illustrates the interplay of these processes in bi-atrial structural remodelling. Similarly reverse remodelling following successful catheter ablation for AF results in a reduction in both LA and RA dimensions³¹. In the present study electrical and structural remodelling in the right atrium correlated with findings in the left atrium in support of the right atrium as representative of the left and consistent with operation of bi-atrial remodelling processes. As such non-clinically indicated RA mapping studies provide useful insights into pathophysiologic processes occurring in the LA.

Clinical implications

There are several important clinical implications. Firstly, there was a significant correlation between the atria supporting assessment of the electrophysiological properties of the RA as a valid surrogate for the LA. As such, the present study supports the conclusions of earlier substrate studies confined to the RA^{4-6, 8}, which demonstrated reductions in tissue voltage with the electrophysiologic sequelae of conduction slowing associated with ageing, heart failure and hypertension. Secondly, this study highlights that persistent AF and its inherent complicit co-

morbidities are not confined to the LA but rather bi-atrial with electrophysiologic changes in part explained by a range of potential mechanisms including atrial stretch^{3,16}, inflammation¹⁷, oxidative stress¹⁸, autonomic neural activity^{19, 20} and the activation of the renin-angiotensin system^{21,22} and sympathetic nervous system. Cardiac MRI using LGE provides a non-invasive assessment of the atria and demonstrates an association between atrial fibrosis, CHADs 2 score and the outcomes of catheter ablation for atrial fibrillation although, to date, the atrial LGE imaging has largely been confined to a single centre³².

Limitations

Several limitations of this study need to be acknowledged. The study population were patients with persistent AF selected for catheter ablation and may not represent the general population with longstanding persistent AF. The patient population were persistent AF patients with a minimum duration of continuous AF of 3 months and as such may limit the generalizability of our findings to paroxysmal AF⁹. However, we selected the persistent AF population as electrical and structural abnormalities are expected and a greater understanding of the atrial substrate in persistent AF may have implications for future substrate modification strategies^{1, 33}. The performance of mapping in sinus rhythm did restrict analysis to patients capable of maintaining sinus rhythm prior to catheter ablation. The conclusions from this study may not apply to conditions such as pulmonary vascular disease or valvular heart disease where direct hemodynamic factors would be expected to result in inherently less equal bi-atrial effects than the systemic effects of AF per se. The predominately male population in this study limits the generalizability of the findings to female AF patients, who may display a gender specific disease profile.

Conclusion

Electrical and structural remodeling within the right atrium correlates with that seen in the left atrium in patients with persistent AF. As such non-clinical mapping studies of the RA provide an important window into the LA without the risks of transeptal access and as such provide useful insights into the mechanisms responsible for atrial fibrillation.

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Legends for Figures

Figure 1 The division of the right and left atria into segment for the purpose of regional analysis.

Figure 2A Bi-atrial global correlation of bipolar and unipolar tissue voltage. Points represent patients with average global bipolar and unipolar values for that patient plotted.

Figure 2B Bi-atrial correlation of low voltage, complex electrograms and conduction velocity (B). Points represent patients with average number of global points reaching defined criteria for complex electrograms (≥ 3 deflections and ≥ 50 ms) and low voltage (< 0.5 mV bipolar) for that patient plotted. For conduction velocity, points represent the global average conduction velocity for each atria in each patient.

Figure 2B

Bi-atrial correlation of low voltage, complex electrograms and conduction velocity

Figure 3: The interplay of physiological processes facilitating bi-atrial structural remodeling in the setting of AF. Several disease states known to be associated with the progression of atrial substrate exert their influence systemically and would exert bi-atrial influence upon remodeling.

Figure 3

The interplay of physiological processes facilitating bi-atrial structural remodeling in the setting of AF

Tables

Table 1 – Baseline Characteristics

Baseline Characteristics n=40	
Age (years)	59 ± 9.2
Gender (% male)	90%
Hypertension	37.5%
Average CHADS ₂ Score	1.1 ± 0.8
Body Mass Index (kg/m ²)	29.1 ± 4.2
Long-lasting Persistent AF (%)	67.5%
Duration of continuous AF pre-ablation (months)	12.9 ± 9.2
Previous DCR	85%
Echocardiographic parameters	
LVEF	44 ± 15%
LA area (cm ²)	28 ± 5.2
LA volume indexed (ml/m ²)	49 ± 14
RA area (cm ²)	25 ± 6.4
Medications	
Beta-blocker	77.5%
ACE Inhibitor	55%
Angiotensin II Receptor Blocker	25%
Mineralocorticoid receptor antagonist	22.5%
Anticoagulation	100%

Table 2 – Global analysis of Electrophysiological Parameters between the RA and LA.

	Right Atrium	Left Atrium	P value	R value	P value
			TTest	Correlation	
Number of points	216 ± 54	220 ± 66	0.76	n/a	n/a
Bipolar Voltage (mV)	1.77 ± 0.57	1.89 ± 0.77	0.45	0.57	<0.001
Unipolar Voltage (mV)	2.28 ± 0.65	2.95 ± 1.14	0.002	0.68	<0.001
Low Voltage <0.5mV (%)	15.7 ± 10.3	15.0 ± 15.7	0.84	0.48	0.002
Complex Electrograms (%)	20.0 ± 14.2	20.0 ± 15.2	0.99	0.73	<0.001
Scar (%)	0.89 ± 2.89	0.79 ± 1.31	0.85		
Conduction velocity (m/s)	0.93 ± 0.15	1.01 ± 0.19	0.02	0.49	0.001
	Right atrium	Left atrium	Bi-atrial	P value	
	X ² test (RA vs LA)				
Scar <0.05mV (% patients)	27.5%	45%	20%	0.10	
Low Voltage (% patients)	95%	88%	95%	0.09	

Table 3: Regional analysis of Tissue voltage and CV between the RA and LA.

	Right Atrium	Left Atrium	P value	R value	P value
Anterior			TTest	Correlation	

Bipolar Voltage (mV)	2.40 ± 0.83	2.10 ± 0.99	0.12	0.31	0.05
Unipolar Voltage (mV)	3.00 ± 0.90	3.24 ± 1.38	0.54	0.54	0.002
Conduction velocity ms⁻¹	0.99 ± 0.20	1.04 ± 0.24	0.26	0.53	<0.001
Posterior					
Bipolar Voltage	1.18 ± 0.48	1.77 ± 0.77	<0.001	0.42	0.007
Unipolar Voltage	1.56 ± 0.54	2.92 ± 1.22	<0.001	0.42	0.006
Conduction velocity ms⁻¹	0.87 ± 0.20	0.95 ± 0.21	0.064	0.29	0.07
Lateral					
Bipolar Voltage	1.86 ± 0.72	2.15 ± 0.90	0.13	0.47	0.002
Unipolar Voltage	2.36 ± 0.84	3.24 ± 1.30	<0.001	0.65	<0.001
Conduction velocity ms⁻¹	0.96 ± 0.21	0.94 ± 0.21	0.69	0.43	0.006
Septal					
Bipolar Voltage	1.51 ± 0.61	1.58 ± 0.84	0.61	0.62	<0.001
Unipolar Voltage	2.11 ± 0.74	2.48 ± 1.32	0.13	0.55	<0.001
Conduction velocity ms⁻¹	0.94 ± 0.21	1.07 ± 0.28	0.003	0.05	0.78

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