Chapter 3

Impact of left atrial fibrosis and left atrial size on the outcome of catheter ablation for atrial fibrillation

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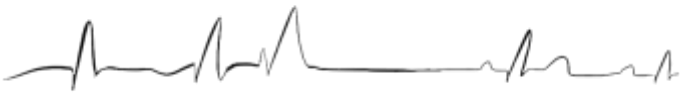

Abstract

Background: Left atrial (LA) dilatation is an important risk factor for recurrence of atrial fibrillation (AF) after radiofrequency catheter ablation (RFCA). However the clinical application to select patients eligible for RFCA according to LA size is limited. Additional pre-procedural assessment of LA fibrosis could improve patient selection for RFCA.

Objective: To investigate the impact of LA size and LA fibrosis on the outcome of RFCA for AF.

Methods: One-hundred-seventy consecutive patients undergoing RFCA for AF were studied. Left atrial size was assessed by measuring maximum LA volume index on echocardiography. LA wall ultrasound reflectivity was assessed by measuring echocardiography derived calibrated integrated backscatter (IBS) as a surrogate of LA fibrosis.

Results: After 12 ± 3 months follow-up, 103 patients (61%) had maintained sinus rhythm and 67 patients (39%) had recurrence of AF. Univariate Cox analyses identified LA wall ultrasound reflectivity, as well as LA size and type of AF, as predictors of AF recurrence after RFCA. Importantly, multivariate analyses showed that LA ultrasound reflectivity remained as strong predictor after correction for LA size and type of AF. Moreover, LA wall ultrasound reflectivity provided an incremental value in predicting outcome of RFCA over LA size and type of AF (increment in global Chi-square 61.6, $p<0.001$).

Conclusion: Assessment of LA fibrosis using two-dimensional echocardiography derived calibrated IBS can be useful to predict AF recurrence after RFCA. Combined assessment of LA fibrosis and LA size improves the identification of patients with a high likelihood for a successful ablation.

Introduction

Radiofrequency catheter ablation (RFCA) is a curative treatment option for patients with symptomatic drug-refractory atrial fibrillation (AF).[1] However, RFCA is associated with a considerable recurrence rate.[2] To improve the outcome of RFCA proper patient selection is mandatory.

Left atrial (LA) enlargement and LA fibrosis are two of the mainstay processes involved in atrial remodeling. LA size is a well recognized risk factor for AF recurrence after RFCA.[3-5] Previous studies have demonstrated that in patients with severe atrial dilatation, the risk for AF recurrence after RFCA is high.[3-5] However, in patients with mild-to-moderate LA enlargement, the AF recurrence rates are still significant and, therefore, the predictive value of LA size is reduced. In addition, LA fibrosis has been related to high probability of AF recurrence after RFCA.[6] Non-invasive evaluation of the extent of atrial remodeling by assessment of LA fibrosis additional to LA size could be used to improve patient selection for AF ablation.

Two-dimensional echocardiography derived integrated backscatter (IBS) allows non-invasive tissue characterization based on tissue ultrasound reflectivity and may provide a good surrogate of myocardial fibrosis.[7,8] Recently, calibrated IBS has been demonstrated to provide a reliable assessment of LA fibrosis.[9]

The aim of this study was to investigate the impact of LA wall ultrasound reflectivity assessed with calibrated IBS (as a surrogate of LA fibrosis) on the outcome of RFCA for AF. In addition, the relative merits of LA size and LA wall ultrasound reflectivity to predict the outcome of RFCA were investigated.

Methods

Patient population and evaluation

One-hundred-and-seventy patients undergoing RFCA for AF were studied. Before the ablation, all patients underwent transthoracic echocardiography to assess LA size, left ventricular (LV) systolic function and to exclude valvular heart disease. In addition, IBS analysis was performed to estimate LA wall ultrasound reflectivity as a surrogate of LA fibrosis. After the ablation, all patients were evaluated at the outpatient clinic during a 12-month follow-up period. Routine electrocardiogram (ECG) recordings were acquired each visit and 24-hour Holter registrations were scheduled after 3, 6 and 12 months follow-up. All medications were continued for at least 3 months. Afterwards, anti-arrhythmic drugs were discontinued at the discretion of the physician. After a blanking period of 3 months, recurrence of AF was defined as any recording of AF on ECG or an episode longer than 30 s on 24-hour Holter monitoring.

Standard echocardiography

Two-dimensional transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid 7, General Electric Vingmed, Milwaukee, WI), equipped with a 3.5-MHz transducer. All patients were imaged in left lateral decubitus position. Two-dimensional and color Doppler data were obtained in the parasternal short- and long-axis views and the apical 2- and 4-chamber views, adjusting gain settings and depth. All images were ECG-triggered and stored in cineloop format for off-line analyses (EchoPac 108.1.5, General Electric Medical Systems, Horten, Norway). Maximum LA volume was obtained from the apical 4- and 2-chamber views by disc's method and indexed to body surface area.[10] Left ventricular ejection fraction was calculated

from the standard apical 2- and 4-chamber views by Simpson's method, according to the American Society of Echocardiography guidelines.[10]

Calibrated integrated backscatter

Integrated backscatter is an echocardiographic parameter based on two-dimensional gray-scale images which measures the myocardial ultrasound reflectivity and can be used to estimate myocardial fibrosis.[11-13] Integrated backscatter is expressed in decibels (dB) and, conventionally, cardiac structures with no fibrotic content have a low ultrasound reflectivity and are coded with negative IBS values (e.g. blood pool) whereas cardiac structures with a high content of fibrosis have a high ultrasound reflectivity and IBS values near 0 dB (e.g. pericardium). Normal myocardium has an intermediate IBS value which increases as the content of fibrosis increases.[8] In the present study, fibrosis of the LA was evaluated by measuring calibrated IBS of the LA wall. For this purpose, two-dimensional gray-scale images were obtained from the parasternal long-axis view, with frame rates between 80 and 120 frames/s. Three cardiac cycles were stored in cine-loop format for offline analysis (EchoPAC 108.1.5, General Electric Medical Systems). A fixed 2 x 3 mm region of interest was positioned in the LA posterior wall, excluding epicardial specular reflections. In addition, the 2 x 3 mm region of interest placed at the pericardium provided the reference value of ultrasound reflectivity to estimate the calibrated IBS value of the LA. Calibrated IBS of the LA was calculated by subtracting the IBS value of the pericardium from the IBS value of the posterior LA wall. Accordingly, higher values (i.e. less negative values) of calibrated IBS correspond to a larger extent of atrial fibrosis. All IBS values were measured during the same phase of the cardiac cycle, at end-diastole.

Radiofrequency catheter ablation

The ablation was aimed at creating circular lesions around the left and right pulmonary vein ostia. All patients received intravenous heparin to maintain an activated clotting time of 300-400 s. Intracardiac echocardiography was used to exclude a cardiac thrombus and to guide the transseptal puncture. A non-fluoroscopic electroanatomical mapping system with multi-slice computed tomography integration was used to guide the ablation procedure (CARTO XP™, Cartomerge™, Biosense Webster, Diamond Bar, CA, USA). Mapping and ablation was performed using a 4-mm quadripolar open-loop irrigated mapping/ablation catheter (7Fr Navistar™, Biosense Webster). Radiofrequency current was applied at 30-35 W with a maximum temperature of 45°C and an irrigation flow of 20 ml/min until a bipolar voltage of <0.1 mV was achieved, with a maximum of 60 s per point. Pulmonary vein isolation was confirmed by recording entrance block during sinus rhythm or pacing in the coronary sinus.[14]

Statistical analysis

All variables were tested for a normal distribution with the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are presented as mean ± SD and were compared with the student's t-test. Continuous variables with a non-normal distribution are presented as median (25^{th}-75^{th} percentile) and statistical comparisons were performed with the Mann-Whitney U-test. Categorical variables are presented as number (percentage) and were compared with the chi-square test. Univariate and multivariate Cox proportional hazard analyses were performed to investigate the relation between calibrated IBS of the LA and risk for AF recurrence after catheter ablation. Variables with a $p<0.05$ in the univariate analyses were included in the multivariate analysis which was performed using an 'enter' method. The incremental value of calibrated IBS of the LA over baseline clinical and

echocardiographic characteristics to assess the risk for AF recurrence was studied by calculating the improvement in global chi-square. Finally, to test the reproducibility of the calibrated IBS measurements, 20 patients were randomly selected to evaluate the inter- and intra-observer variability. The measurements of calibrated IBS of the LA posterior wall were repeated by the same observer in a blinded-fashion and at a separate time (1 week later). To evaluate inter-observer variability, a second independent observer re-analyzed the same dataset. Intra- and inter-observer reproducibility were calculated with the Bland-Altman analysis and the intraclass correlation coefficient. Good correlation was defined as Cronbach's $\alpha > 0.8$. In addition, the test-retest variability of measurement of echocardiographic calibrated IBS was assessed in 20 patients. Two echocardiograms were performed within 24 hours in each patient and the data were analyzed by the same observer. All statistical analyses were performed with SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 170 consecutive patients were included (131 men, mean age 56±9 years), representing an ongoing clinical registry.[15] AF was paroxysmal in 121 patients and persistent in 49 patients according to current guidelines definitions.[16] Median duration of AF was 48 months (interquartile range: 24-96) and the mean number of anti-arrhythmic drugs used was 3.3 ± 1.3 per patient. No patient had previously undergone RFCA for AF. The mean LA volume index was 42.5 ± 15.4 ml/m^2, the mean LA diameter was 42 ± 6 mm and the mean LV ejection fraction was 58 ± 5%. No significant valvular heart disease was observed in any patient. Finally, the mean calibrated IBS of the LA was -18.0 ±

5.1 dB (Table 1). The intra- and inter-observer reproducibility for calibrated IBS measurements were good with small bias and tight limits of agreement (0.93 ± 1.8 dB and 0.12 ± 3.3 dB, respectively) and good intraclass correlation coefficients (0.91 and 0.82, respectively). The test-retest variability for calibrated IBS was 1.07 ± 1.9 dB with an intraclass correlation coefficient of 0.92.

Table 1. Baseline patient characteristics

Patients (n)	170
Age (years)	55.9±9.0
Male gender, n (%)	131 (77)
Body Surface Area (m^2)	2.11±0.20
Type of AF	
Paroxysmal, n (%)	121 (71)
Persistent, n (%)	49 (29)
Duration of AF (months)	48 (24-96)
Number of failed antiarrhythmic drugs (n)	3.3±1.3
Hypertension, n (%)	76 (45)
Hypercholesterolemia, n (%)	51 (30)
Coronary artery disease, n (%)	9 (5)
Beta blocker, n (%)	54 (32)
Class 1 or 3 antiarrhythmic drug, n (%)	132 (78)
ACE inhibitor/angiotensin receptor blocker, n (%)	86 (51)
Diuretic, n (%)	27 (16)
LA volume index (ml/m^2)	42.5 ±15.4
LV ejection fraction (%)	58 ± 5
Calibrated IBS LA (dB)	-18.0±5.1

AF = atrial fibrillation, ACE = angiotensin-converting enzyme, IBS = integrated backscatter, LA = left atrium, LV = left ventricular.

Outcome after radiofrequency catheter ablation

After a mean follow-up of 12 ± 3 months, 103 patients (61%) maintained sinus rhythm, whereas 67 patients (39%) had recurrence of AF. In 22 patients (13%) a repeat procedure was performed due to early recurrence of AF. In the recurrence group a higher prevalence of persistent AF was found compared to

the non-recurrence group (16 [16%] versus 33 [49%], p<0.001). Moreover, in the recurrence group the mean LA volume index and LA diameter were significantly larger compared to the non-recurrence group (46.0 ± 16.9 ml/m^2 versus 40.2 ± 14.1 ml/m^2 [p=0.016] and 44 ± 6 mm versus 41 ± 5 mm [p<0.001], respectively). Patients with persistent AF had significantly higher values (i.e. less negative) of calibrated IBS of the LA than patients with paroxysmal AF (-16.8 ± 4.7 dB versus -18.4 ± 5.2 dB, p=0.049).

To study the relation between LA size, LA calibrated IBS and outcome after RFCA, the study population was divided into 'small LA' subgroup (n=84) and 'large LA' subgroup (n=86) based on the LA volume index, using the mean value (42.5 ml/m^2) as cut-off point. Similarly, the population was divided into 'low fibrosis' subgroup (n=85) and 'high fibrosis' subgroup (n=85) according to calibrated IBS value of the posterior LA wall, using the mean value (-18.0 dB) as cut-off point.

The relation between LA enlargement and calibrated IBS of the LA is shown in Figure 1. Patients in the 'small LA' group had significant lower calibrated IBS values (i.e. more negative) than patients in the 'large LA' group (-19.4 ± 5.0 dB versus -16.5 ± 4.7 dB, p<0.001). Importantly, a wide range of calibrated IBS values was found among patients with a 'small LA', illustrating that a small LA may still contain a large extent of fibrosis content (Figure 1).

Patients in the 'large LA' group had a higher risk for AF recurrence after RFCA than patients in the 'small LA' group (44 [51%] versus 23 [27%], p=0.002) (Figure 2, panel A). When both LA size and LA fibrosis were taken into account, patients with a 'small LA' and 'low fibrosis' (n=52) had the most favorable outcome (94% non-recurrence, p<0.001 vs. others) whereas patients with a 'large LA' and 'high fibrosis' (n=53) had the worst outcome (28% non-recurrence, p<0.001 vs. others). Interestingly, patients with a 'large LA' but with 'low fibrosis' (n=33) had a good prognosis compared to patients with a 'small

LA' and 'high fibrosis' (n=32) (82% non-recurrence vs. 38% non-recurrence, p<0.001) (Figure 2, panel B).

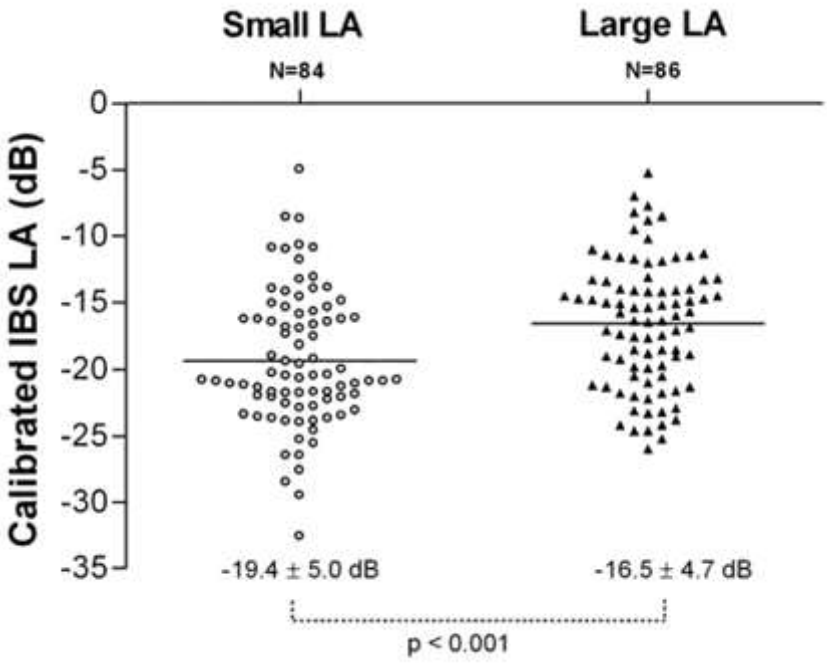

Figure 1. Relation between left atrial (LA) size and calibrated integrated backscatter (IBS) of the LA. 'Small LA' was defined as LA volume index <42.5 ml/m2 and 'large LA' was defined as LA volume index ≥42.5 ml/m2. Importantly, in patients with "small LA", a wide scatter plot was observed indicating a significant proportion of patients with considerable amount of LA fibrosis. Similarly, the group of patients with "large LA" showed a wide range of calibrated IBS values of the LA, but with a mean value significantly higher (i.e. less negative) as compared to the group of patients with "small LA".

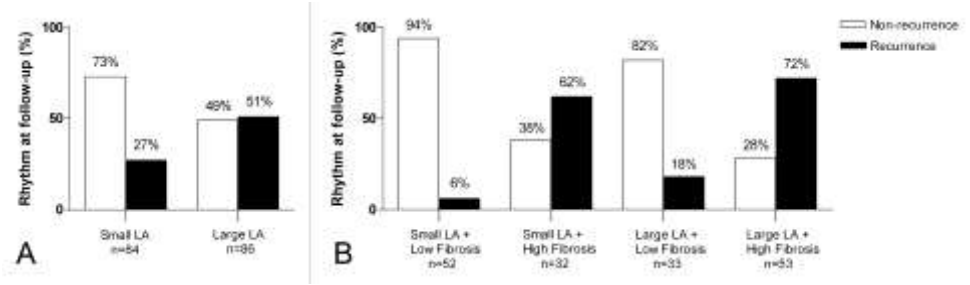

Figure 2. Outcome of radiofrequency catheter ablation (RFCA) according to left atrial (LA) size (panel A) and according to the combination of LA size and LA fibrosis. 'Small LA' was defined as LA volume index <42.5 ml/m2 and 'large LA' was defined as LA volume index ≥42.5 ml/m2. 'Low fibrosis' was defined as calibrated integrated backscatter (IBS) of the LA <-18.5 dB and 'high fibrosis' was defined as calibrated IBS of the LA ≥-18.5 dB. In patients with "small LA" the likelihood of atrial fibrillation (AF) recurrences after RFCA was lower than patients with "large LA". However, the addition of LA fibrosis evaluation permitted a more refined stratification, with higher likelihood of AF recurrence among those patients with "high fibrosis" as compared to patients with "low fibrosis", regardless the LA size (panel B).

Finally, Figure 3 shows the relation between the occurrence of AF recurrence after RFCA and calibrated IBS and LA volume index. Patients who remained in sinus rhythm had significantly lower values of calibrated IBS (i.e. more negative) (-20.6 ± 3.7 dB vs. -13.9 ± 4.0 dB; $p<0.001$) and smaller LA volume index (40.2 ± 14.1 ml/m^2 vs. 46.0 ± 16.9 ml/m^2, $p<0.001$) than patients who had AF recurrences after RFCA. Interestingly, most patients with a value of calibrated IBS >-13.9 dB showed AF recurrence at follow-up. In contrast, there was a significant overlap between LA volume index values of patients who presented with AF recurrences and patients who remained in sinus rhythm and no LA volume cut-off value could be derived to differentiate these two groups of patients. Therefore, calibrated IBS may be a more accurate parameter to identify the patients who will show AF recurrences after RFCA.

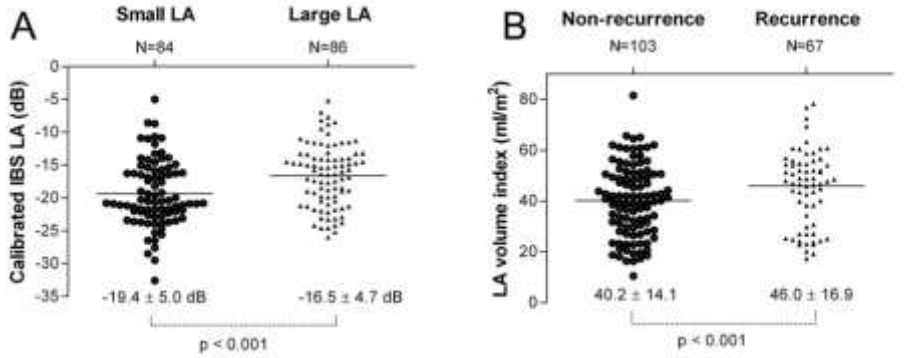

Figure 3. Calibrated integrated backscatter (IBS) of the left atrium (LA) and LA volume index in relation to outcome of radiofrequency catheter ablation. Patients who had atrial fibrillation recurrence after RFCA had significantly higher values of calibrated IBS of the LA (panel A) and LA volume index (panel B) at baseline than patients who remained in sinus rhythm.

Clinical and echocardiographic risk factors for AF recurrence

Univariate and multivariate Cox proportional hazard analyses were performed to evaluate the relation between calibrated IBS of the LA (in combination with other baseline clinical and echocardiographic variables) and the risk for AF recurrence after RFCA. Univariate analyses showed that increased calibrated IBS of the LA (i.e. less negative values) was related to a higher risk for AF recurrence after ablation, as were the presence of persistent AF and enlargement of the LA volume index (Table 2). Multivariate analysis showed that calibrated IBS of the LA was an independent predictor of AF recurrence (HR: 2.796 per 5 dB, 95% CI: 2.168-3.605, $p<0.001$). Moreover, addition of calibrated IBS of the LA to a Cox model including LA volume index and type of AF resulted in a significant improvement in the prediction value for AF recurrence after RFCA (indicated by a significant improvement in global chi-square value: 61.6, $p<0.001$) (Figure 4).

Table 2. Univariate Cox regression analysis of AF recurrence

	HR	95% CI	P-value
Clinical characteristics			
Age (per year)	1.005	0.977-1.033	0.74
Male gender (yes/no)	0.873	0.503-1.514	0.87
AF duration (per month)	1.008	0.959-1.059	0.76
Number of failed antiarrhythmic drugs (per drug)	1.058	0.886-1.262	0.54
Persistent AF (yes/no)	3.264	2.015-5.285	<0.001
Hypertension (yes/no)	1.063	0.658-1.717	0.80
Hypercholesterolemia (yes/no)	1.406	0.856-2.308	0.18
Coronary artery disease (yes/no)	0.217	0.030-1.564	0.13
Echocardiographic characteristics			
Calibrated IBS LA (per 5 dB)	2.670	2.119-3.363	<0.001
LA volume index (per ml/m^2)	1.023	1.006-1.039	0.007
LV ejection fraction (per %)	0.971	0.920-1.024	0.28

AF = atrial fibrillation, IBS = integrated backscatter, LA = left atrium, LV = left ventricular.

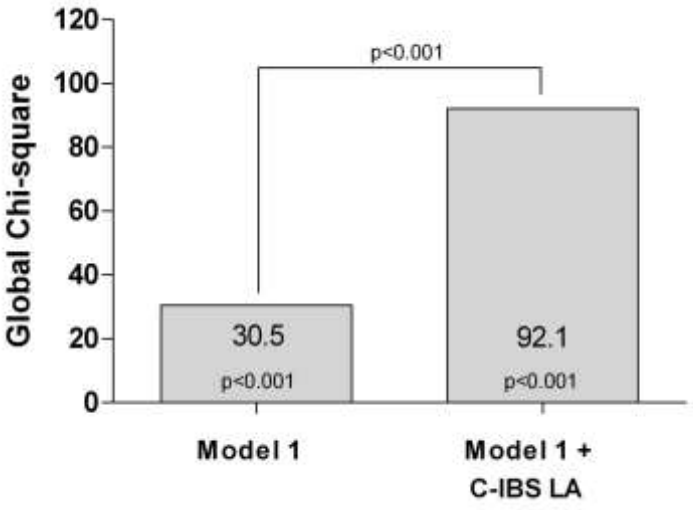

Figure 4. Incremental prognostic value of calibrated integrated backscatter (IBS) of the left atrium (LA). Bar graph illustrating the improvement in global chi-square value by the addition of calibrated IBS of the LA to a Cox regression model comprising LA volume index and type of AF (Model 1).

Discussion

The main findings of the present study were that LA enlargement was related to an increased risk for AF recurrence. More important, a high value of LA calibrated IBS as a surrogate of large extent of LA fibrosis was associated with poor outcome after RFCA. Finally, this study demonstrated that the combined assessment of LA calibrated IBS and LA size improved the identification of patients with a high likelihood for a successful ablation.

Atrial remodeling and outcome: LA size

Atrial fibrillation causes electrical and structural remodeling of the atria which play an important role in the perpetuation and progression of the arrhythmia.[17,18] More importantly, atrial remodeling is associated with a limited efficacy of RFCA for AF.[6] Pre-procedural evaluation of the extent of atrial remodeling can be used to improve patient selection for RFCA.

Atrial dilatation is associated with atrial remodeling.[19] LA size has been shown to be an important risk factor for AF recurrence after RFCA.[3,4] In a group of 148 patients, Berruezo et al. demonstrated that a large anterior-posterior LA diameter was related to a high risk for AF recurrence after RFCA.[3] This was confirmed by Shin et al. who demonstrated that LA volume was an independent predictor of AF recurrence.[4] However, the clinical value of LA size to select patients for RFCA may be limited. Whereas patients with severely enlarged LA may be accurately identified as 'high risk' for AF recurrence, patients with mild-to-moderate LA enlargement show a varying response to RFCA. Accordingly, extensive research has been performed to obtain additional parameters to better predict the outcome of RFCA for AF.

Atrial remodeling and outcome: LA fibrosis

Atrial fibrosis has been proposed as one of the processes involved in atrial remodeling.[20] Moreover, the presence of LA fibrosis is a risk factor for AF recurrence after RFCA.[6] In 700 patients undergoing RFCA for AF, Verma et al. evaluated the extent of LA fibrosis by invasive voltage mapping of the left atrium. The presence of areas with low voltage in the LA (i.e. LA fibrosis) were an independent predictor AF recurrence after RFCA.[6] However, ideally the assessment of LA fibrosis would be performed using a non-invasive and widely available imaging technique prior to the RFCA procedure. Calibrated IBS analysis allows non-invasive tissue characterization based on the quantification of ultrasound energy reflected by scattering elements inside the myocardium.[8,11-13] Recently, assessment of LA fibrosis using calibrated IBS has been validated by Wang et al. in a group of 74 patients undergoing coronary artery bypass surgery.[9] The authors found a good correlation between calibrated IBS value of the LA and the extent of collagen inside the LA appendage. Similarly, in the present study two-dimensional transthoracic echocardiography derived calibrated IBS was used to assess LA fibrosis. Patients with large LA size had higher values of calibrated IBS than patients with a small LA size. However, a large variation existed in the values of LA calibrated IBS in relation to LA size, and a considerable proportion of patients with a small LA had a high values of LA calibrated IBS suggesting a large amount of fibrosis. Notably, patients with small LA and high values of LA calibrated IBS had a significant percentage of AF recurrences at follow-up. Indeed, LA wall ultrasound reflectivity was a strong independent predictor of AF recurrences after RFCA and had an incremental value over LA size. Consequently, assessment of LA calibrated IBS in addition to LA size may improve the selection of patients eligible for RFCA for AF, thereby increasing the procedural success rate.

The assessment of macroscopic LA fibrosis with contrast-enhanced magnetic resonance imaging (CE-MRI) has been recently demonstrated. [21,22] The high spatial resolution of CE-MRI permits exact localization of areas of macroscopic fibrosis within the LA wall. However, CE-MRI is not widely available and, in patients with renal dysfunction, the use of contrast may be not recommended.[23] In contrast, calibrated IBS provides a surrogate of fibrosis content of the LA wall. This analysis is performed on two-dimensional echocardiographic data and no contrast media is needed. Importantly, the present study shows that in combination with assessment of the LA size, calibrated IBS of the LA can be a valuable tool to identify patients with a high likelihood to have AF recurrence after RFCA.

Clinical implications

The present study demonstrated that pre-procedural assessment of LA fibrosis using calibrated IBS analyses can be useful to predict the outcome of RFCA for AF. LA fibrosis can be readily evaluated with this non-invasive imaging technique. Particularly in combination with measurement of LA size, pre-procedural assessment of LA fibrosis improves identification of patients with a high likelihood to maintain sinus rhythm after RFCA. Furthermore, this study extended the evidence that persistent AF is a risk factor for AF recurrence after RFCA. However, the present study also demonstrated that assessment of LA fibrosis with calibrated IBS improved patient selection compared to established risk factors as persistent AF and LA size. Consequently, an improved patient selection could result in a higher success rate of RFCA for AF. Alternatively, this information could be used to better inform patients about their likelihood to maintain sinus rhythm after RFCA.

Limitations

Left atrial fibrosis can be inhomogeneous in patients with AF.[21,22] The inclusion of histological data or the use of other "gold standard" techniques to estimate LA fibrosis (e.g. electroanatomical voltage maps or late-gadolinium enhanced magnetic resonance imaging) would have strengthened our conclusions. Nevertheless, current studies have demonstrated a strong relationship between the measurement of IBS in a single area of the LA and the fibrosis content quantified by histology.[9] In addition, calibrated IBS analyses are dependent on the settings used during image acquisition (e.g. ultrasound frequency, focus, depth, etc).

Conclusion

Assessment of LA fibrosis using two-dimensional echocardiography derived calibrated IBS can be useful to select patients for RFCA for AF. Combined assessment of LA fibrosis and LA size improves the identification of patients with a high likelihood for a successful ablation.

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