EDITOR'S CHOICE

ORIGINAL ARTICLE

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

Dennis W den Uijl, Victoria Delgado, Matteo Bertini, Laurens F Tops, Serge A Trines, Nico R van de Veire, Katja Zeppenfeld, Martin J Schalij, Jeroen J Bax

Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to
Jeroen J Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; j.j.bax@lumc.nl

Accepted 25 January 2011
Published Online First 25 February 2011

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 applications to select patients eligible for RFCA according to LA size is limited. Additional pre-procedural assessment of LA fibrosis might 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 and seventy consecutive patients undergoing RFCA for AF were studied. LA 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 wall ultrasound reflectivity remained a 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 χ^2=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 wall ultrasound reflectivity 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 core processes involved in atrial remodelling. LA size is a well recognised 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 a high probability of AF recurrence after RFCA.[6] Non-invasive evaluation of the extent of atrial remodelling 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 characterisation based on tissue ultrasound reflectivity and may provide a good surrogate of myocardial fibrosis.[7 8] Recently, calibrated IBS has been shown 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.

PATIENTS AND 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 systolic function and to exclude valvular heart disease. In addition, IBS analysis was performed to estimate the 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 h Holter registrations were scheduled after 3, 6 and 12 months' follow-up. All drugs were continued for at least 3 months. Afterwards, antiarrhythmic drugs were discontinued at the discretion of the doctor. 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 h Holter monitoring.

Standard echocardiography

Two-dimensional transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid 7, General Electric Vingmed, Milwaukee, Wisconsin, USA), equipped with a 3.5 MHz transducer. All patients were imaged in the left lateral decubitus position. Two-dimensional and colour Doppler data were obtained in the parasternal short- and long-axis views and the apical two- and four-chamber views, adjusting gain settings and depth. All images were

ECG-triggered and stored in cine-loop format for offline analyses (EchoPac 108.1.5, General Electric Medical Systems, Horten, Norway). Maximum LA volume was obtained from the apical four- and two-chamber views by the disc method and indexed to body surface area.[10] Left ventricular ejection fraction was calculated from the standard apical two- and four-chamber views by Simpson's method, according to the American Society of Echocardiography guidelines.[10]

Calibrated integrated backscatter

Calibrated IBS is an echocardiographic parameter based on two-dimensional grey-scale images, which measures the myocardial ultrasound reflectivity and can be used to estimate myocardial fibrosis.[11–13] IBS is expressed in decibels (dB) and, conventionally, structures with no fibrosis content have a low ultrasound reflectivity and are coded with negative IBS values (eg, blood pool), whereas cardiac structures with a high content of fibrosis have a high ultrasound reflectivity and IBS values near 0 dB (eg, pericardium). Normal myocardium has an intermediate IBS value, which increases as the content of fibrosis increases.[8] In this study, fibrosis of the left atrium was evaluated by measuring calibrated IBS of the LA wall. For this purpose, two-dimensional grey-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 2×3 mm region of interest was positioned in the LA posterior wall, excluding epicardial specular reflections. In addition, the 2×3 mm region of interest placed at the pericardium provided the reference value of ultrasound reflectivity to estimate the calibrated IBS value of the left atrium. Calibrated IBS of the left atrium was calculated by subtracting the IBS value of the pericardium from the IBS value of the posterior LA wall. Accordingly, higher values (ie, 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 trans-septal puncture. A non-fluoroscopic electroanatomical mapping system with multislice CT integration was used to guide the ablation procedure (CARTO XP, Cartomerge, Biosense Webster, Diamond Bar, California, 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 t test. Continuous variables with a non-normal distribution are presented as median (25th–75th centile) and statistical comparisons were performed with the Mann–Whitney U test. Categorical variables are presented as number (percentage) and were compared with the χ^2 test. Univariate and multivariate Cox proportional hazard analyses were performed to investigate the relation between calibrated IBS of the left atrium 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 left atrium over baseline clinical and echocardiographic characteristics to assess the risk for AF recurrence was studied by calculating the improvement in global χ^2. Finally, to test the reproducibility of the calibrated IBS measurements, 20 patients were randomly selected to evaluate the inter- and intraobserver variability. Measurements of the 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 interobserver variability, a second independent observer reanalysed the same dataset. Intra- and interobserver 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 obtained within 24 h in each patient and the data were analysed by the same observer. All statistical analyses were performed with SPSS software (version 16.0, SPSS Inc). 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 (IQR 24–96) and the mean number of antiarrhythmic 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 left ventricular ejection fraction was 58±5%. No significant valvular heart disease was seen in any patient. Finally, the mean calibrated IBS of the LA was −18.0±5.1 dB (table 1). The intra- and interobserver 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

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)
Hypercholesterolaemia, n (%)	51 (30)
Coronary artery disease, n (%)	9 (5)
β 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.

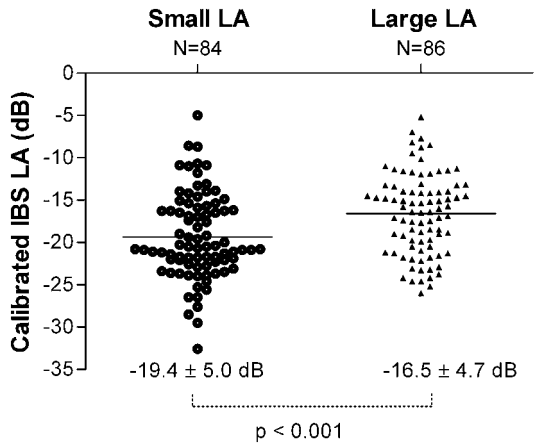

Figure 1 Relation between left atrial (LA) size and calibrated integrated backscatter (IBS) of the LA. 'Small LA' was defined as LA volume index <42.5 ml/m^2 and 'large LA' was defined as LA volume index ≥ 42.5 ml/m^2. Importantly, in patients with "small LA", a wide scatter plot was observed indicating 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 (ie, less negative) than that of the group of patients with "small LA".

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.

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 owing to early recurrence of AF. In the recurrence group a higher prevalence of persistent AF was found compared with the non-recurrence group (16 (16%) vs 33 (49%), p<0.001). Moreover, in the recurrence group the mean LA volume index and LA diameter were significantly larger than in the non-recurrence group (46.0±16.9 ml/m^2 vs 40.2±14.1 ml/m^2 (p=0.016) and 44±6 mm vs 41±5 mm (p<0.001), respectively). Patients with persistent AF had significantly higher values (ie, less negative) of calibrated IBS of the left atrium than patients with paroxysmal AF (−16.8±4.7 dB vs −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 left atrium is shown in figure 1. Patients in the 'small LA' group had significant lower calibrated IBS values (ie, 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 left atrium 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%) vs 23 (27%), p=0.002) (figure 2A). When both LA size and LA fibrosis were taken into account, patients with a 'small LA' and 'low fibrosis' (n=52) had the most favourable 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 with patients with a 'small LA' and 'high fibrosis' (n=32) (82% non-recurrence vs 38% non-recurrence, p<0.001) (figure 2B).

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 (ie, 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.

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 left atrium (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 left atrium (ie, 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

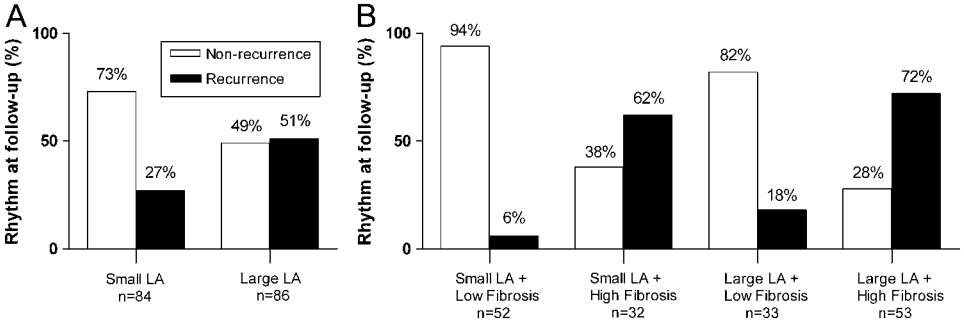

Figure 2 Outcome of radiofrequency catheter ablation (RFCA) according to left atrial (LA) size (A) and according to the combination of LA size and LA-calibrated integrated backscatter (IBS). 'Small LA' was defined as LA volume index <42.5 ml/m^2 and 'large LA' was defined as LA volume index ≥ 42.5 ml/m^2. 'Low fibrosis' was defined as calibrated 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 in 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 with patients with "low fibrosis", regardless of the LA size (B).

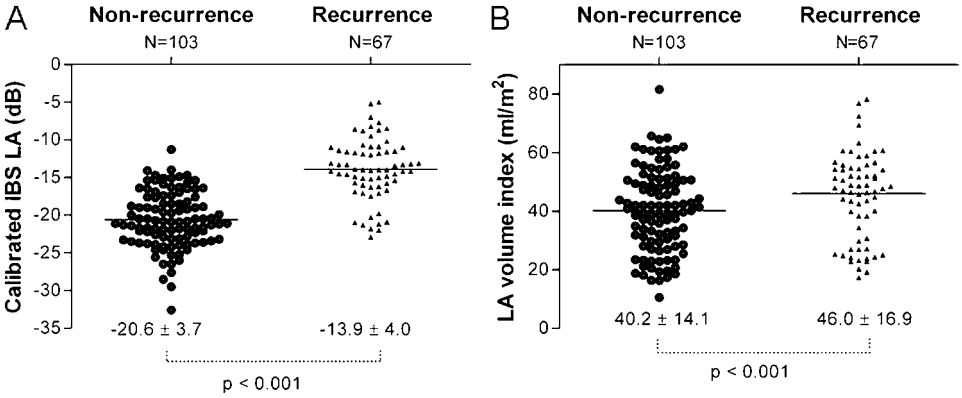

Figure 3 Calibrated integrated backscatter (IBS) of the LA and left atrial (LA) volume index in relation to outcome of radiofrequency catheter ablation (RFCA). Patients who had atrial fibrillation recurrence after RFCA had significantly higher values of calibrated IBS of the LA (A) and LA volume index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

index (table 2). Multivariate analysis showed that calibrated IBS of the left atrium was an independent predictor of AF recurrence (HR=2.796 per 5 dB, 95% CI 2.168 to 3.605, p<0.001). Moreover, addition of calibrated IBS of the left atrium 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 χ^2 value: 61.6, p<0.001) (figure 4).

DISCUSSION

The main findings of this 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 remodelling and outcome: LA size

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

Atrial dilatation is associated with atrial remodelling.[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 a severely enlarged left atrium 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 remodelling and outcome: LA fibrosis

Atrial fibrosis has been proposed as one of the processes involved in atrial remodelling.[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 left atrium (ie, LA fibrosis) were an independent predictor of AF recurrence after RFCA.[6] However, ideally the assessment of LA fibrosis would be performed using a non-invasive and widely available imaging technique before the RFCA procedure. Calibrated IBS analysis allows non-invasive tissue characterisation 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 the calibrated IBS value of the left atrium and the extent of collagen inside the LA appendage. Similarly, in this study two-dimensional transthoracic echocardiography-derived calibrated IBS was used to

Table 2 Univariate Cox regression analysis of AF recurrence

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

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

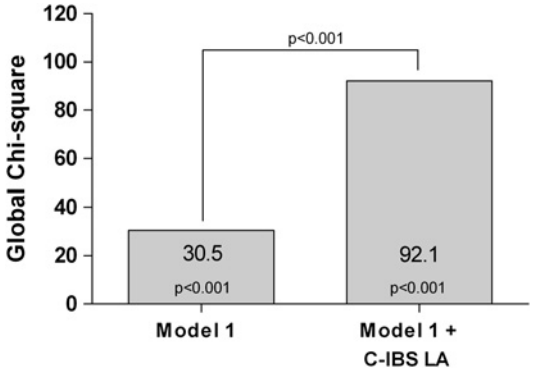

Figure 4 Incremental prognostic value of calibrated integrated backscatter (IBS) of the LA. Bar graph illustrating the improvement in global χ^2 value by the addition of calibrated IBS of the LA to a Cox regression model comprising left atrial (LA) volume index and type of atrial fibrillation (model 1).

assess LA fibrosis. Patients with a 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 left atrium had high values of LA calibrated IBS, suggesting large amount of fibrosis. Notably, patients with a small left atrium 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, measurement 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 MRI (CE-MRI) has been recently demonstrated.[21 22] The high spatial resolution of CE-MRI permits exact localisation of areas of macroscopic fibrosis within the LA wall. However, CE-MRI is not widely available and, in patients with severe renal dysfunction, the use of contrast may be not recommended.[23] In contrast, calibrated IBS provides a surrogate of LA fibrosis. This analysis is performed on two-dimensional echocardiographic data and no contrast media are needed. Importantly, this study shows that in combination with assessment of the LA size, calibrated IBS of the left atrium can be a valuable tool to identify patients with a high likelihood to have AF recurrence after RFCA.

Clinical implications

This 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 calibrated IBS 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, this study also demonstrated that assessment of LA fibrosis with calibrated IBS improved patient selection compared with established risk factors such as persistent AF and LA size. Consequently, 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 of maintaining sinus rhythm after RFCA.

Limitations

LA 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 (eg, electroanatomical voltage maps or late-gadolinium enhanced MRI) would have strengthened our conclusions. Nevertheless, current studies have demonstrated a strong relationship between the measurement of IBS in a single area of the left atrium and the fibrosis content quantified by histology.[9] In addition, calibrated IBS analyses are dependent on the settings used during image acquisition (eg, 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.

Funding MJS receives research grants from Boston Scientific, Medtronic and Biotronik. JJB receives research grants from General Electric Healthcare, Bristol-Myers Squibb Medical Imaging, St Jude, Medtronic, Boston Scientific, Biotronik, and Edwards Lifesciences.

Competing interests None to declare.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Pappone C,** Oreto G, Rosanio S, *et al*. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001;**104**:2539–44.
2. **Cappato R,** Calkins H, Chen SA, *et al*. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005;**111**:1100–5.
3. **Berruezo A,** Tamborero D, Mont L, *et al*. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007;**28**:836–41.
4. **Shin SH,** Park MY, Oh WJ, *et al*. Left atrial volume is a predictor of atrial fibrillation recurrence after catheter ablation. *J Am Soc Echocardiogr* 2008;**21**:697–702.
5. **Hof I,** Chilukuri K, rbab-Zadeh A, *et al*. Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation? *J Cardiovasc Electrophysiol* 2009;**20**:1005–10.
6. **Verma A,** Wazni OM, Marrouche NF, *et al*. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol* 2005;**45**:285–92.
7. **Perez JE,** Barzilai B, Madaras EI, *et al*. Applicability of ultrasonic tissue characterization for longitudinal assessment and differentiation of calcification and fibrosis in cardiomyopathy. *J Am Coll Cardiol* 1984;**4**:88–95.
8. **Picano E,** Pelosi G, Marzilli M, *et al*. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. *Circulation* 1990;**81**:58–64.
9. **Wang GD,** Shen LH, Wang L, *et al*. Relationship between integrated backscatter and atrial fibrosis in patients with and without atrial fibrillation who are undergoing coronary bypass surgery. *Clin Cardiol* 2009;**32**:E56–61.
10. **Lang RM,** Bierig M, Devereux RB, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–63.
11. **Yuda S,** Fang ZY, Marwick TH. Association of severe coronary stenosis with subclinical left ventricular dysfunction in the absence of infarction. *J Am Soc Echocardiogr* 2003;**16**:1163–70.
12. **Mottram PM,** Haluska B, Yuda S, *et al*. Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. *J Am Coll Cardiol* 2004;**43**:848–53.
13. **Wong CY,** O'Moore-Sullivan T, Leano R, *et al*. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004;**110**:3081–7.
14. **Calkins H,** Brugada J, Packer DL, *et al*. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2007;**4**:816–61.
15. **Tops LF,** Bax JJ, Zeppenfeld K, *et al*. Effect of radiofrequency catheter ablation for atrial fibrillation on left atrial cavity size. *Am J Cardiol* 2006;**97**:1220–2.
16. **Fuster V,** Ryden LE, Cannom DS, *et al*. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;**48**:854–906.
17. **Wijffels MC,** Kirchhof CJ, Dorland R, *et al*. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;**92**:1954–68.
18. **Ausma J,** Litjens N, Lenders MH, *et al*. Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. *J Mol Cell Cardiol* 2001;**33**:2083–94.
19. **Sung SH,** Chang SL, Hsu TL, *et al*. Do the left atrial substrate properties correlate with the left atrial mechanical function? A novel insight from the electromechanical study in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:165–71.
20. **Allessie M,** Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;**54**:230–46.
21. **McGann CJ,** Kholmovski EG, Oakes RS, *et al*. New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. *J Am Coll Cardiol* 2008;**52**:1263–71.
22. **Oakes RS,** Badger TJ, Kholmovski EG, *et al*. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* 2009;**119**:1758–67.
23. **Kribben A,** Witzke O, Hillen U, *et al*. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol* 2009;**53**:1621–8.