Indexed left atrial volume predicts the recurrence of non-valvular atrial fibrillation after successful cardioversion

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Aims	Atrial fibrillation (AFib) induces remodelling of the left atrium (LA). Indexed LA volume (iLAV) as more accurate measure of LA size has not been evaluated as predictor of recurrence of AFib after cardioversion.
Methods and results	We identified 411 adults (mean age 64.1 ± 11.4 years, 34.5% women) who underwent successful cardioversion and with no history of other atrial arrhythmia, stroke, congenital heart disease, valvular dysfunction, surgery, thyroid dysfunction, acute or chronic inflammatory disease, and pacemaker. All echocardiographic data were retrieved from the laboratory database. iLAV was measured off-line using Simpson's method. Clinical characteristics and recurrence of clinical AFib were determined by review of medical records. Patients with scheduled follow-up of at least 6 months were included. About 250 patients (60.8%) developed AFib recurrence after a median (25th–75th percentile) follow-up of 345.0 (210.0–540.0) days. Patients with AFib recurrence had significantly greater iLAV than patients without AFib recurrence (39.7 ± 8.4 vs. 31.4 ± 4.6, $P < 0.001$). Each mL/m^2 increase in iLAV was associated with a 30% increased risk of AFib recurrence [odds ratio (OR) 1.30, confidence interval (CI) 1.23–1.38, $P < 0.001$]. In a multivariable model, each mL/m^2 increase in iLAV was independently associated with a 21% increase in the risk of AFib recurrence (OR 1.21, CI 1.11–1.30, $P < 0.001$). The areas under receiver operating characteristic curves, generated to compare LA diameter and iLAV as predictors of AFib recurrence, were 0.59 ± 0.3 and 0.85 ± 0.2, respectively ($P < 0.001$).
Conclusion	The present study is the first to show that larger iLAV before cardioversion, as a more accurate measure of LA remodelling than LA diameter, is strongly and independently associated with higher risks of AFib recurrence.
Keywords	Atrial fibrillation • Cardioversion • Left atrial remodelling • Left atrial volume • Recurrence

Introduction

Atrial fibrillation (AFib) is the most common cardiac rhythm disturbance, increasing in prevalence with age and accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. It is a major cause of stroke and is associated with a two-fold increase in mortality and with a marked reduction in everyday functioning and quality of life.[1] Despite the use of potent anti-arrhythmic drugs, AFib recurrence after cardioversion remains common,[2] leading to serial cardioversion strategy. Several clinical and echocardiographic variables have been reported to predict AFib recurrence in patients after successful cardioversion,[3–5] but their role is still debated. Among these, M-mode antero-posterior left atrial diameter (AP-LAd), a unidimensional measure of LA size, was shown to be incremental to clinical risk factors for predicting AFib.[3,6,7] Although this measurement has been widely used in clinical practice and research, it inaccurately represents true LA size.[8,9] LA volume (LAV) determination is preferred because it allows a more accurate assessment of the asymmetric remodelling of the LA and it is a stronger predictor of cardiovascular outcomes than linear LA dimension.[8] Nevertheless, its role in predicting recurrence of AFib after successful

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cardioversion has never been examined in this clinical setting. Furthermore, the association between LAV indexed to body surface area (iLAV) and AFib recurrence had never been investigated. Therefore, the aims of the present study are to fill these gaps in knowledge by investigating whether iLAV predicts AFib recurrence after successful cardioversion (pharmacological or direct current) and whether it is incremental to clinical risk factors and AP-LAd.

Methods

Study population

All medical records of two Cardiology Clinics (the Cardiology Department of Modena University Hospital and the Civil Hospital of Sassuolo, Italy) were carefully reviewed to identify subjects who underwent a successful direct-current or pharmacological cardioversion for AFib between January 2005 and January 2009. Exclusion criteria were history of other atrial arrhythmias, stroke, congenital heart disease, moderate-to-severe valvular heart disease (including mitral valve prolapse), thyroid dysfunction, chronic obstructive pulmonary disease, acute (within 1 month before and at any time after cardioversion) or chronic inflammatory disease, and any time cardiac surgery. Because surgical treatment may represent itself a trigger for AFib and because the mechanism underlying post-operative AFib is different from other types of AFib,[10] we excluded patients who underwent all types of surgery within 3 months before and at any time after cardioversion. We excluded also patients who received permanent pacemaker at any time before or after the date of cardioversion. We included patients who had successful restoration of sinus rhythm after cardioversion and who had a transthoracic echocardiographic examination within 3 months before the cardioversion.

Clinical data

All medical records were reviewed for clinical data on AFib risk factors at the time of echocardiogram before cardioversion, and these included age, sex, hypertension, diabetes mellitus, hyperlipidaemia, smoking, family history of cardiovascular disease, medical history of cardiovascular disease, duration of the AFib before cardioversion, noting if it was of unknown duration, and previous episode(s) of AFib, noting if it was symptomatic for acute heart failure. Hypertension, diabetes mellitus, hyperlipidaemia, smoking, and family history of cardiovascular disease were defined according to the latest guidelines.[11] Lone AFib was defined as AFib in young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiac and pulmonary disease, with no evidence of hypertension, diabetes mellitus, and thyroid disease.[1] The type of cardioversion and the antiarrhythmic drug used for pharmacological cardioversion were recorded. All direct-current cardioversions were performed using biphasic defibrillator; the total amount of joule and anti-arrhythmic drugs used for facilitation (when performed) were recorded. Pharmacological therapy after cardioversion, including anti-arrhythmic drugs and the so-called 'upstream therapy' for AFib recurrence prevention which encompasses angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, and polyunsaturated fatty acids, was also noted. Data collections and LA size assessment were performed in a blinded fashion.

Echocardiographic data

Digitally stored images of the echocardiograms were retrieved for off-line LA size measurement. LAV was assessed off-line with Simpson's method using apical four-chamber and apical two-chamber views at ventricular end-systole[9] and indexed to body surface area calculated using the Du Bois and Du Bois formula.[12] Inter-operator variability of our laboratory in assessing LA size has been published previously.[13] For AP-LAd assessment, the mean difference between the measurements was 0.2 ± 2.0 mm and interclass correlation coefficient was 99.1%; for LAV, inter-observer mean difference was 0.2 ± 5.5 mL and interclass correlation coefficient was 98.4%, both indicating outstanding reliability. Patients with suboptimal images that precluded the assessment of LAV were excluded. All echocardiographic studies were performed according to the American Society of Echocardiography standards.[9] Left ventricular (LV) ejection fraction was assessed by the biplane Simpson method or by the Quinones method using the LV end-systolic and end-diastolic diameters[14] or visually estimated, a method that was documented to have an accuracy comparable to the other methods in assessing LV ejection fraction.[15] Mitral regurgitation was assessed semi-quantitatively by colour Doppler as absent, mild, moderate, or severe. All other echocardiographic data were retrieved from the computerized echocardiography databases.

Outcomes ascertainment

Follow-up for AFib recurrence was performed by review of all medical records starting at the time of cardioversion. After cardioversion, all patients were scheduled for follow-up visit, including 12-lead ECG at 1, 6, and 12 months and at least one 24 h Holter ECG within 6 months. To define AFib recurrence, confirmation by ECG was required. No distinction was made between paroxysmal and persistent AFib recurrence. Patients with a scheduled follow-up of at least 6 months were included.

Statistical analysis

Results are presented as mean $\pm$ SD for continuous variables and as frequency (percentages) for categorical variables. Group comparisons were performed using the t-test or χ^2 test, as appropriate. Logistic regression analysis was used to identify univariate and multivariable predictors of AFib recurrence; the odds ratio (OR) and 95% confidence interval (CI) are shown. Receiver operating characteristic (ROC) curves were generated to compare M-mode AP-LAd and iLAV as predictors of recurrence of AFib after cardioversion. The areas under the ROC curves were compared using the method of DeLong et al.[16] All tests are two-sided, and $P < 0.05$ was considered to be significant. Statistical analysis was conducted using SPSS 15.0 and Medcalc 7.3.

Results

Baseline characteristics and clinical predictors of atrial fibrillation recurrence

We identified 628 subjects who underwent successful cardioversion for AFib between January 2005 and January 2009 at both centres. After review of the medical records, 158 patients were excluded because of the presence of exclusion criteria. In addition, 59 patients were excluded because LA dimension had not been measured in the original study or appropriate images for LAV assessment were not available. The remaining 411 patients (mean age 64.1 ± 11.4 years, 34.5% women) represent the study population.

Termination of the arrhythmia was achieved with pharmacological cardioversion in 97 (23.6%) and with direct-current cardioversion in 313 (76.2%) patients. Pharmacological cardioversion was

obtained with amiodarone in 47 (11.4%), flecainide in 19 (4.6%), and propafenone in 5 patients (1.2%). In 66 (16.1%) patients, electrical cardioversion was performed with pre-medication with amiodarone in 47 (10.2%), propafenone in 39 (9.5%), and flecainide in 11 (2.7%).

For the overall cohort, 250 patients (60.8%) developed AFib recurrence after a median (25th–75th percentile) follow-up of 345.0 (210.0–540.0) days. Baseline clinical characteristics of patients, stratified by AFib recurrence status at follow-up, are presented in *Table 1*. Patients who subsequently developed AFib recurrence were older and were more likely to have hypertension,

diabetes, history of previous AFib, AFib symptomatic for acute heart failure, and longer AFib duration. Patients with AFib recurrence were more likely to have unknown arrhythmia duration before cardioversion.

Echocardiographic predictors of atrial fibrillation recurrence

Patients with AFib recurrence had significantly greater iLAV than those without AFib recurrence (39.7 ± 8.4 vs. 31.4 ± 4.6, $P <$ 0.001). Furthermore, they had larger M-mode AP-LAd, lower ejection fraction, worse degree of mitral regurgitation, larger LV

Table 1 Characteristics of the study population at baseline

	No AFib recurrence, n=161 (39.2%)	AFib recurrence, n=250 (60.8%)	*P*-value
Clinical characteristics			
Age (years)	60.8 ± 12.4	66.2 ± 10.3	<0.001
Sex (female)	52 (32.3)	90 (36.0)	0.44
Body mass index (kg/m²)	26.9 ± 4.4	26.8 ± 4.3	0.95
Body surface area (m²)	1.80 ± 0.25	1.76 ± 0.24	0.10
Hypertension	126 (78.3)	226 (90.4)	0.001
Smoke	46 (28.6)	75 (30.0)	0.76
Family history of CAD	41 (25.5)	84 (33.6)	0.08
Dyslipidaemia	55 (34.2)	89 (35.6)	0.76
Diabetes	11 (6.8)	36 (14.4)	0.02
CAD	24 (14.9)	35 (14.0)	0.80
Previous AFib	51 (31.7)	112 (44.8)	0.008
AFib symptomatic for AHF	15 (9.3)	41 (16.4)	0.04
AFib duration (days)	9.4 ± 16.7	20.6 ± 28.1	<0.001
Unknown AFib duration	4 (2.5)	28 (11.2)	0.01
Characteristics of CV			
Pharmacological CV	45 (28.0)	48 (19.2)	0.04
	Amiodarone 25 (15.5)	Amiodarone 20 (8.0)	
	Flecainide 2 (1.2)	Flecainide 9 (3.6)	
	Propafenone 18 (11.2)	Propafenone 19 (7.6)	
Direct-current CV	115 (71.4)	198 (79.2)	0.07
Total amount of joule	173.0 ± 115.3	222.0 ± 125.8	0.001
Direct-current CV with anti-arrhythmic drugs facilitation	15 (9.3)	51 (20.4)	0.03
	Amiodarone 12 (2.9)	Amiodarone 30 (7.4)	
	Flecainide 2 (0.4)	Flecainide 17 (4.2)	
	Propafenone 1 (0.2)	Propafenone 4 (0.9)	
Anti-arrhythmic drugs and upstream therapy after CV			
Amiodarone	30 (18.6)	61 (24.4)	0.17
IC class	99 (61.5)	173 (69.2)	0.10
Sotalol	3 (1.9)	5 (2.0)	0.92
ACE-I	50 (31.1)	95 (38.0)	0.15
ARBs	74 (46.0)	120 (48.0)	0.69
Statin	62 (38.5)	101 (40.4)	0.70
Beta-blockers	105 (65.2)	189 (76.2)	0.01
Digitalis	8 (5.0)	30 (12.0)	0.02
PUFA	9 (5.6)	17 (6.8)	0.62

AFib, atrial fibrillation; CAD, coronary artery disease; AHF, acute heart failure; CV, cardioversion; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; PUFA, polyunsaturated fatty acid.

dimension, and higher degree of LV hypertrophy (Tables 2 and 3, echocardiographic characteristics). Each mL/m^2 increase in iLAV was associated with a 30% increased risk of AFib recurrence (OR 1.30, CI 1.23−1.38, $P < 0.001$). When iLAV was categorized according to ASE/EAE recommendation for chamber quantification cut-offs, there was a progressive increase in the cumulative risk of AFib recurrence from normal to severe iLAV enlargement (Figure 1).

Multivariable predictors of atrial fibrillation recurrence

In a multivariable logistic regression model, iLAV was significantly and independently predictive of AFib recurrence after adjusting for age, sex, hypertension, diabetes, family history of cardiovascular disease, history of previous AFib, AFib symptomatic for acute heart failure, AFib duration, ejection fraction, AP-LAd, mitral regurgitation, LV hypertrophy, LV enlargement, and medical therapy (Table 4). Each mL/m^2 increase in iLAV was independently associated with a 21% increase in the risk of AFib recurrence (adjusted OR 1.21, CI 1.11−1.30, $P < 0.0001$). Other multivariable predictors of AFib recurrence resulted in age, previous AFib, AFib with symptoms of acute heart failure, AFib duration and unknown AFib duration, and LV hypertrophy degree. Notably, at univariate analysis, AP-LAd was associated with an increased risk of AFib recurrence (Table 3, echocardiographic characteristics); however when both AP-LAd and iLAV were simultaneously included in the multivariable model, AP-LAd was no longer significant (Table 4). After further adjustment for anti-arrhythmic drugs and upstream therapy, iLAV remained associated with significantly increased risks of AFib recurrence (adjusted OR 1.20, CI 1.11− 1.30, $P < 0.0001$).

Table 2 Baseline echocardiographic characteristics of the study population

Variable	No AFib recurrence n = 161 (39.2%)	AFib recurrence n = 250 (60.8%)	P-value
iLAV (mL/m^2)	31.4 ± 4.6	39.7 ± 8.4	<0.001
AP-LAd (mm)	37.8 ± 4.0	39.8 ± 5.3	<0.001
EF (%)	57.4 ± 6.6	55.4 ± 7.3	0.003
Mitral regurgitation	No 95 (59.0) Mild 63 (39.1) Mild−moderate 3 (1.9)	No 119 (47.6) Mild 113 (45.2) Mild−moderate 18 (7.2)	0.005
Left ventricular enlargement	No 156 (96.9) Mild 5 (3.1) Moderate 0 (0.0)	No 222 (88.8) Mild 18 (7.2) Moderate 10 (4.0)	0.002
Left ventricular hypertrophy	No 127 (78.9) Mild 33 (20.5) Moderate 1 (0.6)	No 73 (29.2) Mild 120 (48.0) Moderate 57 (22.8)	<0.001

AFib, atrial fibrillation; iLAV, indexed left atrial volume; AP-LAd, M-mode antero-posterior left atrial diameter.

Indexed left atrial volume and lone atrial fibrillation

In 59 (14.3%) patients who met criteria for lone AFib, mean iLAV was significantly lower than that of the rest of the AFib patients (31.2 ± 4.5 vs. 36.7 ± 8.3 mL/m^2, respectively, $P < 0.001$). Of these, 24 patients had AFib recurrence (Table 5). The only two

Table 3 Univariate model

	OR	95% CI	P-value
Clinical characteristics			
Age (1-year increase)	1.04	1.02−1.06	<0.001
Sex (female)	0.85	0.56−1.29	0.44
Body mass index (kg/m^2)	1.00	0.96−1.05	0.95
Body surface area (m^2)	0.45	0.22−1.10	0.10
Hypertension	2.62	1.49−4.59	0.001
Smoke	0.93	0.60−1.44	0.76
Family history of CAD	0.67	0.43−1.05	0.08
Dyslipidaemia	1.06	0.70−1.61	0.76
Diabetes	2.29	1.13−4.65	0.02
CAD	1.08	0.61−1.90	0.80
Previous AFib	1.75	1.16−2.65	0.008
AFib symptomatic for AHF	1.90	1.02−3.58	0.04
AFib duration (days)	1.02	1.01−1.03	<0.001
Unknown AFib duration	4.95	1.70−14.39	0.001
Echocardiographic characteristics			
iLAV (1 mL/m^2 increase)	1.30	1.23−1.38	<0.001
AP-LAd (mm)	1.09	1.05−1.14	<0.001
EF (%)	0.95	0.92−0.99	0.003
Mitral regurgitation (°)	1.64	1.16−2.32	0.006
Left ventricular enlargement (°)	3.47	1.46−8.24	0.05
Left ventricular hypertrophy (°)	7.0	4.58−10.72	<0.001
Characteristics of CV			
Pharmacological CV	0.60	0.38−0.96	0.03
Direct-current CV	1.52	0.96−2.40	0.07
Total amount of joule	1.004	1.001−1.006	0.001
Direct-current CV with anti-arrhythmic drugs facilitation	2.49	1.35−4.6	0.03
Anti-arrhythmic drugs and upstream therapy after CV			
Amiodarone	1.41	0.86−2.30	0.17
Ic class anti-arrhythmic drugs	1.40	0.92−2.13	0.11
Sotalol	1.07	0.25−4.56	0.92
ACE-I	1.36	0.89−2.07	0.15
ARBs	1.08	0.73−1.61	0.69
Statin	1.08	0.72−1.62	0.70
Beta-blockers	1.72	1.11−2.67	0.01
Digitalis	2.60	1.16−5.84	0.02
PUFA	1.23	0.53−2.83	0.62

AFib, atrial fibrillation; OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; AHF, acute heart failure; CV, cardioversion; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; PUFA, polyunsaturated fatty acid.
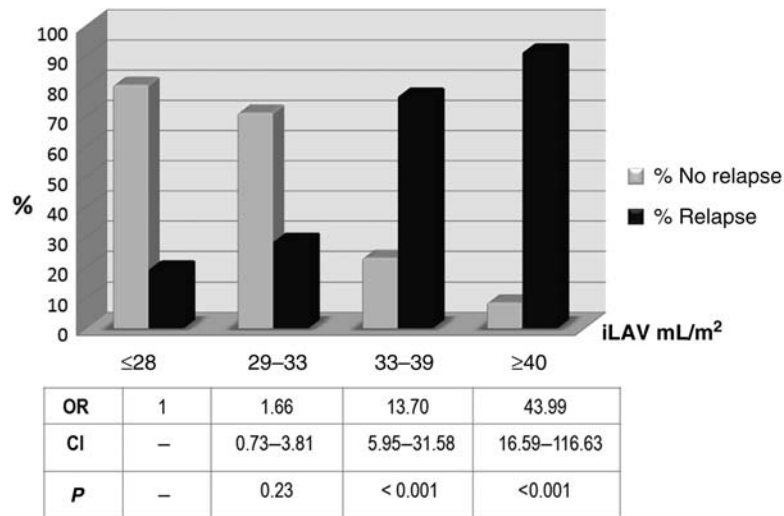
Figure 1 Progressive increase in the cumulative risk of AFib recurrence from normal to severe iLAV enlargement. iLAV categorized according to ASE/EAE recommendation for chamber quantification cut-offs. AFib, atrial fibrillation; OR, odds ratio; CI, confidence interval; AP-LAd, M-mode antero-posterior left atrial diameter; iLAV, indexed left atrial volume.

Table 4 Multivariable predictors of atrial fibrillation recurrence

	OR	95% CI	P-value
iLAV (1 mL/m^2 increase)	1.21	1.11–1.30	<0.0001
Age (1-year increase)	1.03	1.00–1.06	0.04
Sex (female)	0.82	0.47–1.43	0.50
Body mass index (kg/m^2)	0.96	0.90–1.04	0.32
Hypertension	0.40	0.16–1.02	0.07
Family history of CAD	1.53	0.85–2.77	0.16
Diabetes	1.26	0.48–3.28	0.63
Previous AFib	2.10	1.15–3.84	0.02
AFib with symptoms of AHF	0.71	0.25–2.01	0.52
AFib duration (1-day increase)	1.01	1.00–1.03	0.04
Unknown AFib duration	2.90	0.76–11.20	0.12
Ejection fraction	1.03	0.97–1.11	0.34
AP-LAd (1 mm increase)	0.97	0.91–1.04	0.36
Mitral regurgitation	0.79	0.45–1.37	0.40
Left ventricular enlargement	2.66	0.55–12.92	0.23
Left ventricular hypertrophy	2.52	1.26–5.01	0.01

AFib, atrial fibrillation; OR, odds ratio; CI, confidence interval; iLAV, indexed left atrial volume; CAD, coronary artery disease; AHF, acute heart failure; AP-LAd, M-mode antero-posterior left atrial diameter.

Table 5 Characteristics of patients with 'lone' atrial fibrillation

	No AFib recurrence, n = 35 (59.3%)	AFib recurrence, n = 24 (40.7%)	P-value
Age (years)	46.6 ± 12.4	51.0 ± 7.1	0.3
Sex (female)	10 (28.6)	4 (16.7)	0.3
Previous AFib	12 (34.3)	11 (45.8)	0.4
AFib duration (days)	5.1 ± 7.8	12.3 ± 15.6	0.02
AP-LAd (mm)	37.7 ± 5.1	38.0 ± 3.6	0.8
iLAV (mL/m^2)	29.9 ± 3.7	33.1 ± 4.9	0.01

AFib, atrial fibrillation; AP-LAd, M-mode antero-posterior left atrial diameter; iLAV, indexed left atrial volume.

increase was associated with a 27% increased risk (adjusted OR 1.27, 95% CI 1.06–1.52, $P = 0.01$).

Receiver operating characteristic curves analysis

ROC curves were generated to compare M-mode AP-LAd and iLAV as predictors of recurrence of AFib after cardioversion (*Figure* 2). The area under the curve was 0.85 ± 0.2 for iLAV vs. 0.59 ± 0.3 for AP-LAd ($P < 0.001$). The best discriminating value of iLAV to predict AFib recurrence was 33.5 mL/m^2, which was characterized by an 83% sensitivity and 76% specificity. The cut-off value for severe iLAV enlargement (40 mL/m^2) corresponded to a 38% sensitivity and 96% specificity. An iLAV of 50 mL/m^2 was 100% specific as predictor of AFib recurrence, although the sensitivity decreased to 25%.

predictors of AFib recurrence were iLAV and AFib duration. AP-LAd was not a significant predictor of AFib recurrence. At univariate analysis, each mL/m^2 increase in iLAV was associated with a 21% increased risk of AFib recurrence (OR 1.21, 95% CI 1.04–1.53, $P = 0.01$). In a multivariable model including age, sex, history of previous AFib, AFib duration, and AP-LAd, iLAV remained the best predictor of AFib recurrence; each mL/m^2
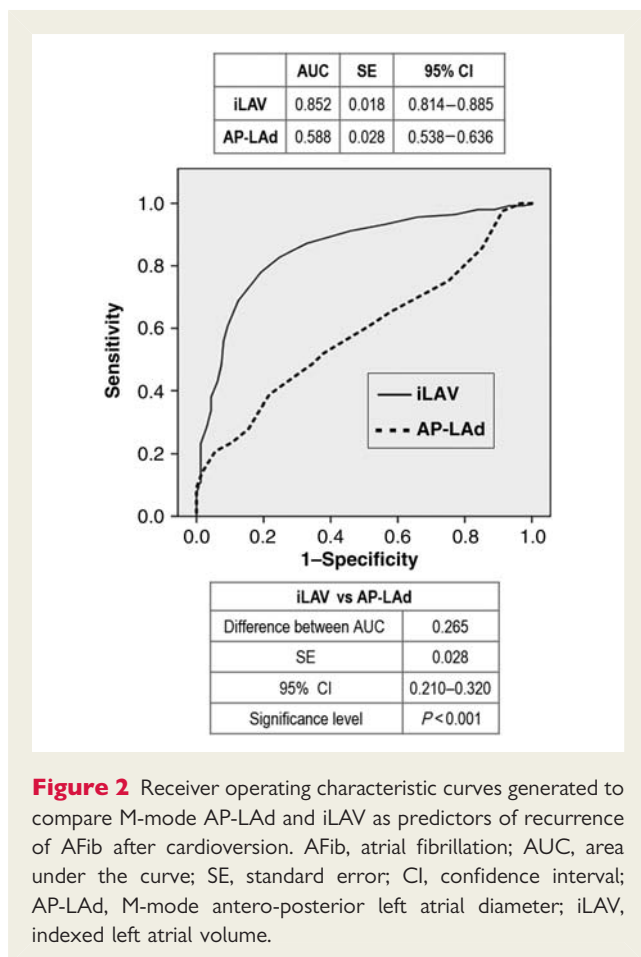
Figure 2 Receiver operating characteristic curves generated to compare M-mode AP-LAd and iLAV as predictors of recurrence of AFib after cardioversion. AFib, atrial fibrillation; AUC, area under the curve; SE, standard error; CI, confidence interval; AP-LAd, M-mode antero-posterior left atrial diameter; iLAV, indexed left atrial volume.

Discussion

The present study is the first to show that iLAV measured before cardioversion is a significant and independent predictor of AFib recurrence. It is incremental to clinical risk factors and M-mode AP-LAd. Despite the emerging evidence that iLAV is a better predictor of a first episode of AFib than AP-LAd,[17–19] few studies evaluating the determinants of AFib recurrence after cardioversion focused on AP-LAd.[3,20,21] No studies examined the role of iLAV as predictor of AFib recurrence after cardioversion. Our group previously demonstrated that the assessment of LA size by iLAV allows identification of patients with enlarged atria that would have been missed if classified by AP-LAd.[13]

For the optimal use of echocardiographic LA size in AFib risk stratification, the method used for accurate quantification is pivotal.[22] Measurement of AP linear LA dimension by M-mode echocardiography is easy and rapid, but not reliably accurate, given that the LA is not spherically shaped. The expansion of the LA in the AP dimension may be constrained by the thoracic cavity between the sternum and the spine. Predominant enlargement in the superior–inferior and medial–lateral dimensions alters LA geometry such that the AP dimension may not be representative of LA size. Conversely, biplane iLAV by two-dimensional echocardiography provides a more accurate and reproducible estimation of LA size when compared with reference standards such as magnetic resonance imaging[23] and three-dimensional echocardiography.[24]

Accordingly, the ASE/ESC have recommended quantification of LA size by biplane volumetric two-dimensional echocardiography using either the Simpson method or the area–length method which are comparable in accuracy and reproducibility.[9]

Despite this growing evidence, the latest guidelines for AFib management[1] have included LA size assessment just in terms of M-mode AP dimension. The present study supports that iLAV provides more information than AP-LAd in terms of global LA remodelling.

Left atrial remodelling as predictor of atrial fibrillation recurrence

The concept of LA remodelling is definitely in evolution.[25] It refers to a time-dependent adaptive regulation of cardiac myocytes in order to maintain homeostasis against external 'stressors'. The type, extent, and reversibility of atrial remodelling depend on the strength and the duration of exposure to the stressors. The most common stressors of atrial myocytes include volume/pressure overload and tachycardia. Increased volume/pressure overload leads to chamber dilatation and stretch of the atrial myocardium, providing the substrate for AFib to be sustained.[25] Tachycardia-induced LA remodelling is mostly reversible, even if prolonged high rates of cell depolarization make restoring and maintaining sinus rhythm less likely.[26,27]

The volume/pressure overload and tachycardia-induced remodelling are not mutually exclusive and usually may coexist at various times in the same patient. The structural changes of the LA reflect an average effect of LV filling pressures over time due to reduced LV compliance rather than an instantaneous measurement at the time of the study.[22] This is common in various conditions such as hypertension, diabetes, coronary artery disease, and chronic heart failure,[28] supporting the hypothesis that AFib may be a symptom of an underlying LV disease. According to these findings,[25] the present study shows that hypertension, diabetes, LV hypertrophy, lower ejection fraction, and LV enlargement are associated with high probability of AFib recurrence. Particularly, LV hypertrophy results in a strong and independent predictor of AFib relapse even in the multivariable model. However, iLAV resulted superior to clinical risk factors in predicting AFib recurrence, probably because LA remodelling represents the final and macroscopic result of the sum of each single clinical predictor.

It is hard and intriguing to establish which one is the point of no-return. We have compared the percentage of patients who relapse on the basis of the iLAV enlargement cut-offs, and we have observed that there are no significant differences between the normal and mildly dilated LA. The risk of AFib recurrence increases significantly for iLAV >33.5 mL/m^2. This is quite the same as the value reported by previous studies that have evaluated the role of iLAV as predictor of major cardiovascular events and mortality.[22] It is likely that some grade of irreversibility begins in the range of moderate iLAV enlargement. As expected, the larger the iLAV, the more the risk of AFib recurrence (*Figure 1*), probably because of the higher grade of LA fibrosis. Even in lone AFib patients, despite the theoretical absence of cardiac structural abnormalities, atrial fibrosis and LV diastolic dysfunction have been demonstrated.[29,30] Of note, in our entire cohort, we have found 59

(14.3%) patients with lone AFib. This percentage is lower than the 30% recorded in the Alfa study,[31] probably because we enrolled only patients with persistent lone AFib and we did not take into account those with paroxysmal AFib. Although lone AFib may be considered a 'pure atrial disease' and not a consequence of some sort of cardiac dysfunction, we have found that even in lone AFib patients, iLAV is the best predictor of AFib recurrence both at univariate and multivariable analyses, although the mean iLAV in patients with lone AFib recurrence is significantly lower than that of patients with non-lone AFib, likely because of the absence of an underlying structural LV disease.

Strengths and limitations

The major strength of the present study is that it is the first to test the predictive role of volumetric measure of LAV in the post-cardioversion setting. Furthermore, all echocardiographic studies were performed according to the American Society of Echocardiography standards, and inter-operator variability of our laboratory in assessing LAV has been published previously.[13] LAV was indexed to body surface area. Physicians measuring iLAV data off-line were blinded to the clinical data and outcomes of the patients. We have considered only echocardiograms performed at least within 3 months before the cardioversion in order to avoid underestimation of the true LA size. Although this was a retrospective study, the clinical follow-up was scheduled at 1, 6, and 12 months; furthermore, to guarantee a sufficiently long follow-up, we excluded patients with a follow-up of <6 months.

All medical records were carefully reviewed and only clinically documented AFib were considered, thus we cannot exclude that some patients had asymptomatic AFib recurrence. Although we paid attention to thoroughly note all therapies, we cannot evaluate whether such drugs effectively treated AFib risk factors (hypertension, dyslipidaemia, and diabetes) and we could not measure their pleiotropic effects on LA fibrosis or remodelling.

Conclusions

iLAV is a significant and independent predictor of AFib recurrence after successful cardioversion. It is superior to M-mode AP-LAd because it allows a more accurate assessment of the asymmetric remodelling of the LA. Furthermore, iLAV is incremental to clinical risk factors, and medical therapy in predicting AFib recurrence, likely because LA remodelling represents the final and macroscopic result of the sum of each single predictor. Although latest guidelines for AFib management[1] mention LA size assessment just in terms of M-mode AP dimension, the present study encourages the use of iLAV as a valuable tool for the clinician managing patients with AFib. Larger prospective studies are needed to establish iLAV utility in AFib management.

Conflict of interest: none declared.

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