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Original article

Non-invasively estimated left atrial stiffness is associated with short-term recurrence of atrial fibrillation after electrical cardioversion

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ABSTRACT

Background: As atrial stiffness (K_{la}) is an important determinant of cardiac pump function, better mechanical characterization of left atrial (LA) cavity would be clinically relevant. Pulmonary venous ablation is an option for atrial fibrillation (AF) treatment that offers a powerful context for improving our understanding of LA mechanical function. We hypothesized that a relation could be detected between invasive estimation of K_{la} and new non-invasive deformation parameters and traditional LA and left ventricular (LV) function descriptors, so that K_{la} can be estimated non-invasively. We also hypothesized that a non-invasive surrogate of K_{la} would be useful in predicting AF recurrence after cardioversion.
Methods: In 20 patients undergoing AF ablation, LA pressure–volume curves were derived from invasive pressure and echocardiographic images; K_{la} was calculated during ascending limb of V-loop as ΔLA pressure/ΔLA volume. 2D-speckle-tracking echocardiographic LA and LV longitudinal strains and volumes, ejection fraction (EF) and ventricular stiffness (K_{lv}), as obtained from mitral deceleration time, were tested as non-invasive K_{la} predictors. In 128 sinus rhythm patients 1 month after electrical cardioversion for persistent AF, non-invasively estimated K_{la} (*computed*-K_{la}) was tested as predictor of recurrence at 6 months.
Results: Tertiles of mean LA pressure correlated with increasing K_{la} (trend, $p = 0.06$) and decreasing LA peak strain, LVEF, and LV longitudinal strain ($p = 0.029$, $p = 0.019$, and $p = 0.024$). There were no differences in LA and LV volumes and K_{lv} across groups. Multiple regression analysis identified LV longitudinal strain as the only independent predictor of K_{la} ($p = 0.014$). Patients in highest quartile of *computed*-K_{la} (estimated as [log] = 0.735 + 0.051 × LV strain) tended to have highest AF recurrence rate (25%) as compared with remaining 3 quartiles (9%, 9%, 3%, $p = 0.09$).
Conclusion: K_{la} can be assessed invasively in patients undergoing AF ablation and it can be estimated non-invasively using LV strain. AF recurrence after cardioversion tends to be highest in highest quartile of *computed*-K_{la}.

Background

Atrial stiffness (K_{la}) is an important determinant of cardiac pump function. It has been demonstrated that a flexible atrium to the inlet of an artificial heart substantially improves the heart's output [1]. Conversely, an increase in K_{la} should reduce stroke volume and forward flow. Furthermore, left atrial (LA) wall stiffening, as assessed combining LA strain with invasively measured or noninvasively estimated mean pulmonary capillary wedge pressure, has been shown to be accurate in identifying patients with diastolic heart failure [2]. Thus, better mechanical characterization of the LA cavity would be clinically relevant [3], particularly in view of the potential association between LA stiffening and development of atrial fibrillation (AF) recurrences after AF ablation or cardioversion.

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Pulmonary venous ablation is a relatively new option for AF treatment that offers a powerful context for improving our understanding of LA mechanical function. Since transseptal puncture is most commonly performed with transesophageal echocardiographic guidance, LA dimensions and LA pressure–volume data can be obtained simultaneously. It is possible to integrate measurements of LA dimension with recordings of LA pressure, in order to generate pressure-dimension or pressure–volume curves, and from these K_{la} can be calculated during the ascending limb of the V-loop as the ratio of ΔLA pressure and ΔLA volume.

Furthermore, the special context represented by the procedure of pulmonary venous isolation for AF makes it feasible to test correlations between an invasive estimate of K_{la} and new non-invasive LA and left ventricular (LV) functional parameters describing cardiac mechanical characteristics. We hypothesized that a relation could be detected between invasive estimation of K_{la} and new non-invasive deformation parameters and traditional LA and LV function descriptors, so that K_{la} may be estimated non-invasively. We also hypothesized that a non-invasive surrogate of K_{la} would be useful in predicting AF recurrence after electrical cardioversion.

Methods

Invasive evaluation of left atrial stiffness (K_{la}) during atrial fibrillation ablation

Patients

Twenty-five consecutive patients, with no more than mild mitral regurgitation and with persistent or paroxysmal AF resistant to medical therapy, underwent NavX™-guided AF ablation (St Jude Medical, St Paul, MN, USA). Written informed consent was obtained from each patient, in accordance with Institutional Human Studies Committee Guidelines.

Transesophageal echocardiography

Transesophageal echocardiography was performed under light sedation by the imaging cardiologist just before the transseptal puncture [Vivid pro echocardiography machine (GE Medical System, Horten, Norway); 6T, KZ191683 probe, GE Medical System] [4].

Five patients were excluded from the final analysis because of suboptimal echocardiographic views or pressure artifacts, resulting in an overall feasibility of 80% (20 out of 25 patients).

Left atrial volume assessment

LA volume data were calculated from the superior-inferior dimension of the cavity, as imaged from expanded mid-esophageal four- and/or two-chamber views. Superior-inferior dimension was measured by M-mode echocardiography, directing the interrogating beam toward the mitral annulus, close to the anterior leaflet of the mitral valve. The base-to-apex dimension of the LA cavity could thus be defined, on the M-mode tracing, as the distance between a point 0.5 cm below the first echo generated from the surface of the transducer and the mitral annulus [5] and measured continuously during the entire cardiac cycle (Fig. 1A).

The superior-inferior diameter of the LA was obtained off-line by subtraction, after digitization of the superior and inferior boundaries, using a commercially available *ad hoc* software package (Sigmascan, version 5.0 for Windows, Jandel, San Rafael, CA, USA). At least 5 beats per patient were stored; ectopic and immediate post-ectopic beats were excluded from the digitization process.

Sixty-five percent of the patients were in AF at the time of the examination; in these subjects non-consecutive beats were selected to obtain recordings with comparable R-R intervals. A linear interpolation algorithm was then used to normalize each beat to a fixed number of time sampling points ($n = 200$), to enable multiple beats averaging (Fig. 1B).

The LA volume, modeled empirically as a sphere, was estimated by the formula: $V = 0.52 \times D3$, where V is LA volume and D is the superior to inferior dimension of the atrium in the M-mode tracing [6,7].

Left atrial pressure measurement

Time-adjusted LA pressure was measured simultaneously with imaging data using a fluid-filled catheter (0.5–1.3 mm in diameter and 71 cm long, BRK, St Jude Medical) that had been introduced transseptally by the electrophysiologist and sequentially connected to a strain-gauge transducer (Haemofix-Combitrans Monitoring, Braun, Melsungen, Germany). A line [6.0 mm in diameter and 150 cm long (Braun)] with a 3-way stopcock at the end was used to display the pressure tracing on the screen of a physiologic recorder (Tram-Rac A4, Mac-lab 6.0, GE Medical System). The catheter, routinely used in our institution for monitoring LA pressure during AF ablation, was placed under transesophageal guidance, filled with saline, and visually leveled to the right atrium. Continuous LA pressure signals were also visible on the screen of the echo machine (Fig. 1A).

The LA pressure monitoring system had been previously tested in an in vivo animal (pig) model, relative to a micromanometer-tipped catheter (Mikrotip model PC-350, Millar Instruments, Houston, TX, USA). The time-delay of the system relative to the micromanometer catheter (median 50 ms; range 0–60 ms) was subsequently used as a time-correction factor for the LA pressure tracing in our patients. An electrocardiographic (ECG) trace was also recorded in real-time.

The LA volume and pressure traces were then used to generate the LA pressure–volume loop using a commercially available spreadsheet, the transesophageal base-to-apex LA diastolic dimension correlating well with the derived four-chamber LA cavity area ($r = 0.56$, $y = 0.95x + 3.5$, $p = 0.01$, SEE = 0.8 cm).

Left atrial stiffness (K_{la}) was assessed using the pressure–volume loop during the ascending limb of the V-loop and computed as the ratio of ΔLA pressure – from the time of minimal to maximal systolic pressure – and ΔLA volume during this time period (Fig. 1C).

Transthoracic echocardiography

Transthoracic echocardiographic data were acquired within 15 ± 9 days from the ablation procedure using a 3.5 MHz variable-frequency transducer (GE Medical System), as in our previous studies devoted to LA mechanical function [8,9].

LA volume was calculated according to the biplane area-length method: $8/3\pi \times$ [(LA area in apical four-view chamber $\times$ LA area in apical two-chamber)/d], where d is the shorter LA long-axis diameter in apical four- and two-chamber views [10].

LV volumes were obtained by real-time three-dimensional echocardiography using three apical longitudinal planes and then by manually tracing the endocardial border using commercial software excluding the papillary muscles (EchoPAC PC version BT112, GE Healthcare). In order to estimate LV volumes this software constructs a triangular mesh by three-dimensional interpolation between the traces, and end-diastolic and end-systolic volumes are calculated by surface triangulation and summation of all triangles by the divergence theorem [11]. LV ejection fraction (EF) is calculated from the three-dimensional end-diastolic and end-systolic volumes [12]. LV mass was assessed with the two-dimensional area–length formula [13]. LA area and volume, and LV volume and mass were indexed to body surface area. Mitral deceleration time, taken as an index of diastolic

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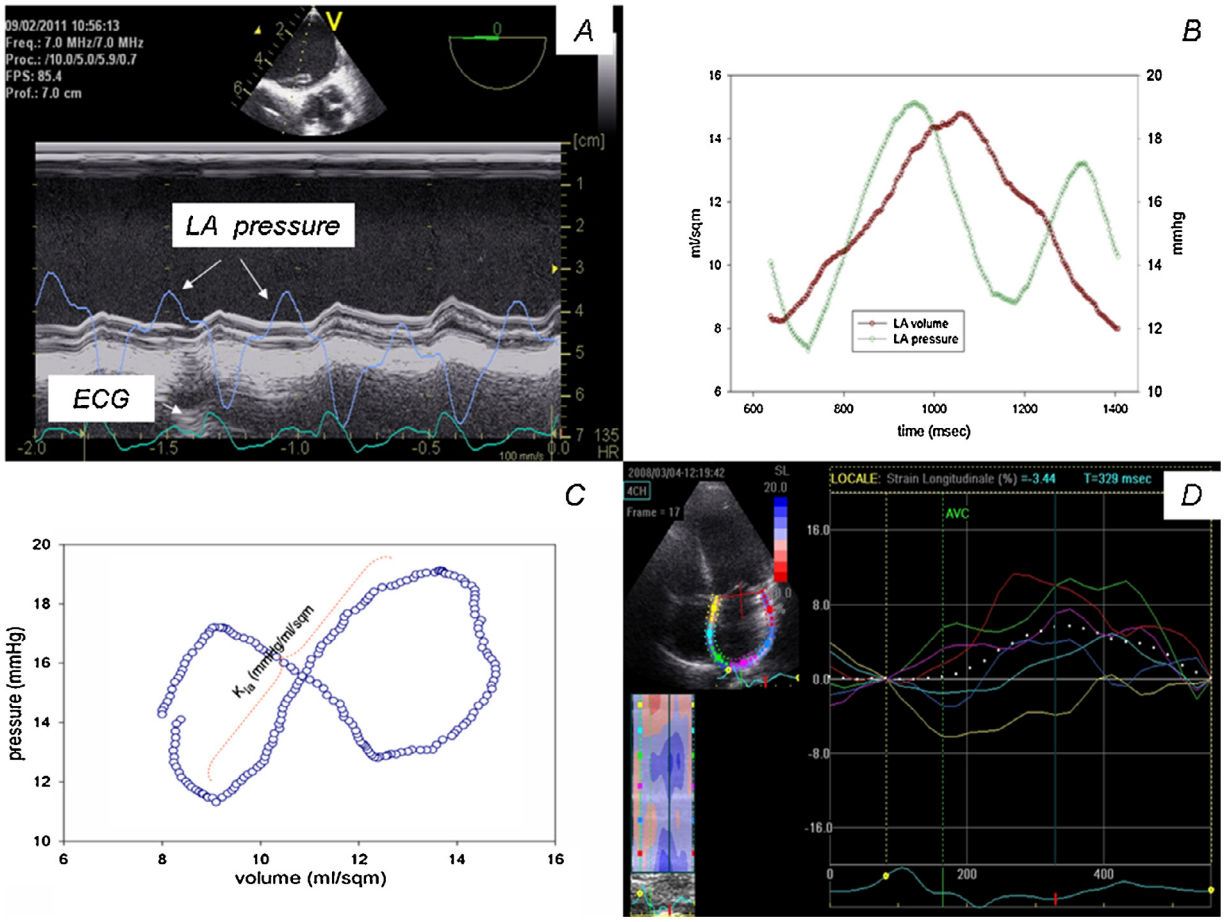

Fig. 1. (A) Transesophageal M-mode recording of the superior-inferior dimension of the LA cavity with a superimposed simultaneous LA pressure and ECG trace. (B) LA pressure curve and computed simultaneous LA volume. (C) LA pressure–volume curve. LA stiffness (K_{la}) is calculated during the ascending limb of the V-loop and computed as the ratio of ΔLA pressure – from the time of minimal to maximal systolic pressure – and ΔLA volume. (D) Example of two-dimensional speckle-tracking based LA strain curves derived from a four-chamber apical view. Each curve represents one of the six LA wall segments; the dotted line is the mean averaged peak LA strain. ECG, electrocardiogram; LA, left atrial.

function, was measured as the time interval between peak E wave and the zero intercept of the deceleration profile. LV stiffness (K_{lv}) was also quantified, according to the following equation ($K_{lv} = 1.28^{\exp[-0.008 \times \text{mitral deceleration time}]}$) that had been previously validated by invasive methods in a group of cardiomyopathic patients [14].

LA longitudinal strain was assessed by using a two-dimensional speckle-tracking technique from standard gray-scale loops [15]. Regional deformation of 6 LA segments located along the interatrial septum, the roof, and the lateral wall of the LA cavity was assessed in the apical four-chamber view starting from the QRS complex, with the average of 6 segments, generally peaking in late systole, as LA peak strain (Fig. 1D).

Longitudinal LV strain was also assessed from the same four-chamber images which were used to evaluate LA strain and was averaged over 6 segments along the ventricular septum, apex, and lateral wall.

Mechanical inhomogeneity within the atrial wall has been reported to reflect structural conditions that predispose to AF recurrences [16]. Thus, atrial dyssynchrony, taken as a measure of such inhomogeneity, was quantified by the standard deviation of the times to peak positive deformation of each atrial strain curve (TP-SD) and expressed as a percentage of the R-R′ interval [8,9]. Time to peaks in opposition phase to the expected direction of strains were not included in the final computation. Values of strain for these segments counted as 100 in averaging strain. High grade of LA dyssynchrony was identified by larger values of TP-SD with corresponding lower values of LA peak strain [16].

Prediction of recurrence of AF after electrical cardioversion in a prospective cohort

We hypothesized that high values of a non-invasive predictor of K_{la} (*computed-*K_{la}), as derived from the relation between invasive estimation of K_{la} and measured new non-invasive strain parameters, besides more traditional LA and LV functional descriptors (*vide infra*), might be associated with AF recurrence after electrical cardioversion in a prospective patients' sample.

In particular, we tested if high values of *computed-*K_{la} could be associated with AF recurrence during a 5-month follow-up period in 128 patients who had had electrical cardioversion because of AF 1 month earlier (71.2 ± 8.7 years, 79 males). These patients had been selected from an original group of 150 consecutive persistent AF patients because they were in sinus rhythm at the 4-week follow-up visit and exhibited satisfactory echocardiographic recordings with LV longitudinal strain data availability, like for those patients who had had invasive K_{la} estimation. The AF etiology was ischemic in 16 patients (13%), hypertensive in 48 (38%), valvular in 9 (7%), cardiomyopathic in 13 (10%), and undetermined in 42 (33%).

After cardioversion all selected patients underwent a 24-h Holter recording at 1, 3, and 6 months, with AF recurrence defined as symptomatic or asymptomatic episodes of atrial arrhythmia

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Table 1
Characteristics of patients undergoing AF ablation ($n = 20$).

Age (years)	66 ± 9
CHA_2DS_2Vasc score	3.9 ± 1.8
Male (%)	55
Body mass index (kg/m^2)	29.0 ± 4.8
Body surface area (m^2)	1.96 ± 0.22
Etiology of AF (%;*n*)	
Ischemic heart disease	10;2
Hypertension	45;9
Valvular heart disease	10;2
Dilated cardiomyopathy	5;1
No structural heart disease – lone AF	30;6
Therapy (*n*)	
Amiodarone	6
Propafenone	2
Flecainide	2
ACE-inhibitors	8
AT-1 receptor blockers	10
Beta-blockers	14
Sotalol	3
Calcium channel blockers	9

AF, atrial fibrillation; CHA_2DS_2Vasc, congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–75 years, sex category [female]; ACE, angiotensin-converting enzyme; AT, angiotensin.

(>30 s, registered AF or flutter or tachycardia on ECG or Holter ECG examinations) causing cardiology consultation.

Statistical analysis

Data are expressed as mean ± SD or median (25th–75th confidence intervals) if data were not normally distributed. Differences among means were assessed by one-way ANOVA or with Kruskal–Wallis ANOVA on ranks, as appropriate. Differences between means were assessed by unpaired *t* tests. A Mann–Whitney rank sum test was used if data were not normally distributed. Differences in percentages were assessed using the chi-square test. Univariate and multivariate backward and forward stepwise regression analyses were used to evaluate the relationship between echocardiographic parameters with significant variations across tertiles of mean LA pressure and K_{la}. Age, history of hypertension and AF duration, besides LA volume, were also evaluated in the multivariate regressions as they are associated with LA fibrosis. A log transformation was used for not normally distributed data.

In order to find a diagnostic cut-off value of *computed*-K_{la}, K_{lv}, and *computed*-$K_{la} + K_{lv}$ for the identification of short-term AF recurrence after cardioversion, nonparametric receiver-operating characteristics (ROC) curve analyses were performed and the area under the curve showing the discriminatory ability of the variable cut-off was reported.

Sensitivity and specificity values of the best cut-off variable were also calculated. A *p*-value <0.05 was considered to be significant. Statistical analyses were performed using Sigma Plot version 12.5 for Windows statistical software (Jandel; San Rafael, CA, USA).

The interobserver variability, expressed as absolute mean difference ± the percentage coefficient of variation (SD/mean) and assessed by analyzing TP-SD and average LA strain before and after cardioversion using the same clips randomly chosen within a comparable patients' population by 2 independent investigators on two different occasions was 1.78% ± 1.02% and 3.56% ± 1.21%, respectively [9]. The same number for LV strain was 3.82% ± 0.80% [17].

Results

Invasive evaluation of left atrial stiffness (K_{la}) during ablation of atrial fibrillation

Transesophageal echocardiographic data were analyzed in 20 patients (14 persistent and 6 paroxymal AF), while on their usual treatment, who underwent AF ablation (7 in sinus rhythm and 13 in AF; mean of 4 ± 1 beats). Their baseline characteristics are summarized in Table 1.

Patients were divided into three groups (3 tertiles) according to increasing values of mean LA pressure (5.6–13.3 mmHg, $n = 6$; 14.3–16.8 mmHg, $n = 7$; 20.4–36.4 mmHg, $n = 7$). K_{la} averaged 2.8 ± 3.3 mmHg/ml/m^2, with values tending to increase across progressive tertiles of mean LA pressure (trend, $p = 0.06$) (Table 2). Conversely LA peak strain, LV longitudinal strain and EF decreased across tertiles ($p = 0.029$, $p = 0.024$, and $p = 0.019$) (Table 2). There were no differences among groups in TP-SD of atrial strains, LA and LV volumes, mitral deceleration time, and K_{lv}. Only LV mass was larger in the highest tertile of LA pressure, as compared with the other two ($p = 0.002$, Table 2).

We demonstrated a linear inverse relation between LA TP-SD and LA peak strain ($r = -0.44$, $p = 0.05$) (Fig. 2, left), with subjects in sinus rhythm generating greater deformation for a given degree of atrial mechanical dispersion. The TP-SD/LA peak strain ratio increased significantly from 1st to 3rd tertile ($p = 0.03$, Fig. 2, right) and correlated directly with K_{la} ($r = 0.52$, $p = 0.019$). There was also an inverse relation between LA peak strain and LV longitudinal strain ($r = -0.54$, $p = 0.014$) and a direct relation between mean LA pressure and LV mass ($r = 0.65$, $p = 0.002$).

Table 2
Assessed variables tertiles of mean left atrial pressure in patients undergoing atrial fibrillation ablation ($n = 20$).

		1st tertile ($n = 6$)	2nd tertile ($n = 7$)	3rd tertile ($n = 7$)	*p*
Mean left atrial pressure	mmHg	8.8 [6.4–10.9]	15.2 [14.7–16.0]	25.0 [23.4–30.7]	<0.001
Left atrial stiffness (K_{la})	mmHg/ml/m^2	0.92 [0.47–1.88]	1.72 [0.79–2.16]	5.08 [1.34–7.79]	0.063
Peak left atrial strain	%	20.2 ± 6.2	13.5 ± 6.2	9.6 ± 7.0	0.029
Left atrial dyssynchrony (TP-SD)	%	12.5 ± 7.5	17.4 ± 4.1	17.8 ± 8.6	0.355
Left atrial volume	ml/m^2	29 [22–36]	36 [22–43]	36 [35–36]	0.432
Left ventricular stiffness (K_{lv})	mmHg/ml/m^2	0.127 [0.10–0.17]	0.127 [0.11–0.18]	0.126 [0.10–0.18]	0.977
Left ventricular longitudinal systolic strain	%	−13.8 ± 3.9	−9.5 ± 4.5	−7.3 ± 3.1	0.024
Left ventricular end-diastolic volume	ml/m^2	57 ± 15	57 ± 12	69 ± 20	0.298
Left ventricular ejection fraction	%	61 ± 12	53 ± 8	42 ± 12	0.019
Left ventricular mass	g/m^2	153 ± 41	144 ± 20	226 ± 49	0.002
Mitral deceleration time	ms	203 ± 51	200 ± 67	188 ± 70	0.891
Body mass index	(kg/m^2)	28.8 ± 3.9	30.3 ± 5.1	27.8 ± 5.9	0.654

K_{la}, atrial stiffness; K_{lv}, ventricular stiffness; TP-SD, time-to-peak standard deviation.

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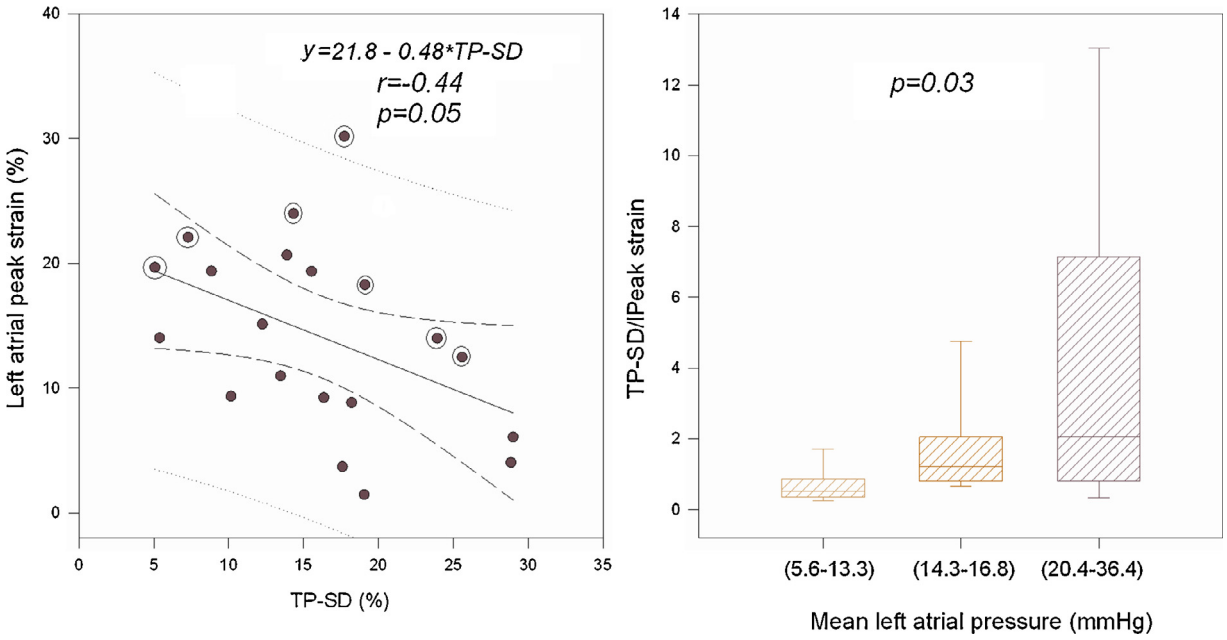

Fig. 2. (Left) Relation between LA TP-SD and peak longitudinal LA strain in patients who underwent pulmonary venous isolation. Patients in sinus rhythm (within circle) before the procedure generate greater deformation for a given degree of atrial mechanical dispersion. (Right) Boxplot of TP-SD/LA peak strain increasing with mean LA pressure. The graph suggests that temporal and mechanical inhomogeneities take place within the atrial wall when tension increases. LA, left atrial; TP-SD, time-to-peak standard deviation.

*Non-invasive estimation of left atrial stiffness (*computed-K_{la}*)*

Univariate regression analyses found LV ejection fraction (EF) ($r = -0.51$, $p = 0.022$), LV longitudinal strain ($r = 0.54$, $p = 0.014$), and LA peak strain ($r = -0.44$, $p = 0.051$) as predictors of K_{la}. Multivariate analysis identified LV longitudinal strain as the only significant independent predictor of K_{la} [$y(\log) = 0.735 + 0.051 \times$ LV longitudinal strain, $\beta = 0.54$, $p = 0.014$], with no significant contribution from the other variables [mean K_{la} predicted: 1.92 ± 0.98 mmHg/ml/m^2 (95% CI: 1.11 ± 0.48 to 3.40 ± 2.24 mmHg/ml/m^2) Table 3, Fig. 3, left]. The results were not changed if TP-SD/LA peak strain ratio ($r = 0.52$, $p = 0.019$ at the univariate analysis) was included in the multivariate analysis instead of LA peak strain (Table 3).

AF ablation

All patients examined were in sinus rhythm at the end of the procedure, with the exception of 2 subjects that could not be reverted from AF and did not reach sinus rhythm within the 3-month period. Two patients developed cardiac tamponade after ablation and were successfully treated with pericardiocentesis, and one subject became hypotensive which resolved with intravenous fluids.

Follow-up after AF ablation

The median value of K_{la} in those patients who maintained sinus rhythm at 3 months ($n = 15$) was 1.34 mmHg/ml/m^2 (0.79–2.16), compared with 5.48 mmHg/ml/m^2 (1.72–7.79) in those ($n = 3$) who had AF recurrence during follow-up (trend, $p = 0.075$). Values for the combination of $K_{la} + K_{lv}$ were 1.39 mmHg/ml/m^2 (0.94–2.27) vs. 5.65 mmHg/ml/m^2 (1.76–7.90), respectively (trend, $p = 0.076$).

Prospective cohort of patients with AF recurrence after electrical cardioversion

The clinical characteristics and medical treatment of the prospective cohort are summarized in Table 4. Drugs that could impact on sinus rhythm maintenance were kept unaltered during follow-up [18].

AF recurrence rate during 5-month follow-up was 12% (15 patients out of 128). The characteristics of patients with AF recurrence, as compared with those who maintained sinus rhythm at 6 months ($n = 113$), are also reported in Table 4, together with treatments potentially affecting rhythm maintenance long-term. LV mass tended to be slightly larger ($p = 0.08$) in patients with AF recurrence. There were no other differences between groups.

Table 3
Univariate and multivariate analysis for prediction of K_{la} in the patients' population who underwent AF ablation procedure ($n = 20$).

Variable	*p* univariate	*p* multivariate	Variable	*p* univariate	*p* multivariate
Left ventricular longitudinal strain	0.014	0.014[a]	Left ventricular longitudinal strain	0.014	0.014[a]
Left ventricular ejection fraction	0.022	0.239	TP-SD/LA peak strain ratio	0.019	0.168
Left atrial peak strain	0.051	0.387	Left ventricular ejection fraction	0.022	0.239
Left atrial volume		0.508	Left atrial volume		0.508
Duration of AF		0.453	Duration of AF		0.453
Hypertension		0.342	Hypertension		0.342
Age		0.164	Age		0.164

AF, atrial fibrillation; LA, left atrial; TP-SD, time-to-peak standard deviation.
[a] Variable included in the final model.

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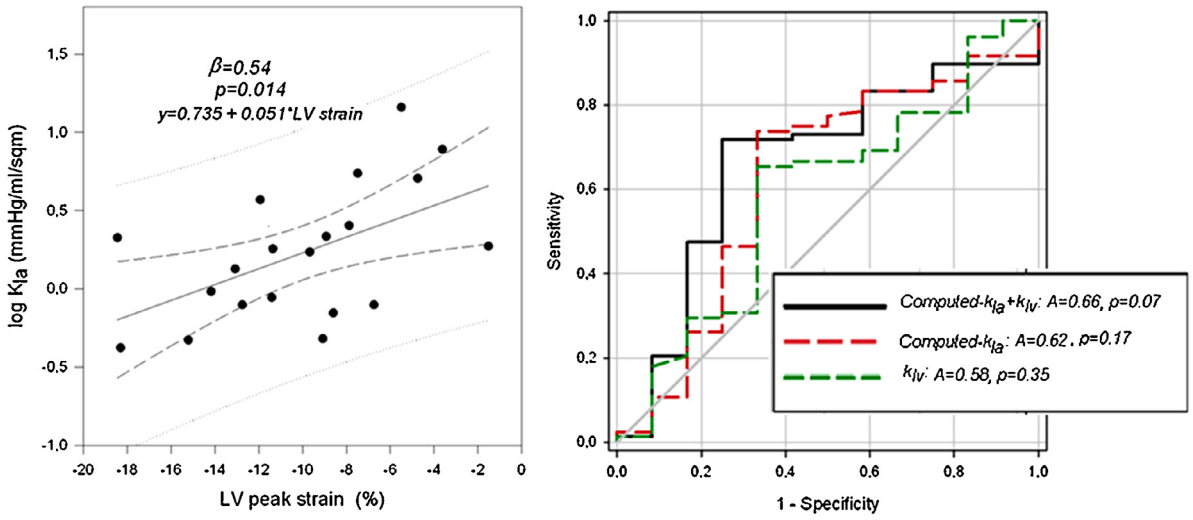

Fig. 3. (Left) Relation between LV peak strain (*x*-axis) and invasively-derived LA stiffness (K_{la}) scaled logarithmically (*y*-axis) in patients who underwent pulmonary venous ablation. There is a significant, direct relation between the 2 parameters ($p = 0.014$). (Right) Receiver-operating characteristics curve analysis for the identification of short-term (6 months) recurrence of atrial fibrillation. K_{la}, atrial stiffness; K_{lv}, ventricular stiffness; LA, left atrial; LV, left ventricular.

Variables of the prospective cohort arranged according to increasing quartiles of *computed*-K_{la}, as obtained from the multivariate analysis according to the formula: *computed*-K_{la} (log) = 0.735 + 0.051 × LV longitudinal strain, are reported in Table 5. There was a progressive decline in LA peak strain ($p = 0.004$) and a consequent increment in the TP-SD/LA peak strain ratio ($p = 0.039$) across quartiles of *computed*-K_{la}, but there were no differences in LA volume, age, CHA_2DS_2Vasc score, and body mass index. As expected from the progressive shortening of mitral deceleration time (trend, $p = 0.08$), K_{lv} increased across quartiles, similarly to *computed*-K_{la} (Table 5).

The incidence of AF recurrences tended to be larger (25%) in the highest quartile of *computed*-K_{la} as compared with the remaining 3 quartiles (9%, 9%, and 3% respectively, trend, $p = 0.09$) (Table 5). The combination of *computed*-K_{la} + K_{lv} for the 3 highest quartiles collapsed together exhibited a ROC curve area of 0.66 ($p = 0.07$) in identifying short-term (5 months) AF recurrence after cardioversion, with 72% sensitivity and 75% specificity for a value of 1.43 mmHg/ml/m^2 (Fig. 3, right). The same analysis for either factor alone (ROC curve area for *computed*-K_{la}: 0.62, $p = 0.17$ and for K_{lv}: 0.58, $p = 0.35$) was not significant.

Discussion

In the present study we observed a linear relationship between LV longitudinal strain and an invasive descriptor of the mechanical profile of the LA cavity, K_{la}. This association suggests that information obtainable from LV longitudinal strain might be used to estimate the mechanical characteristics or stiffness of the left atrium.

It is a widely accepted concept that there is an association between the longitudinal deformation of the left atrium and the

Table 4
Characteristics, assessed variables, and treatment in the entire patients' population followed-up after electrical cardioversion ($n = 128$) and divided according to rhythm at 6 months.

		Entire population ($n = 128$)	Sinus rhythm ($n = 113$)	AF recurrence ($n = 15$)	p[a]
Age	years	73 [67–77]	74 [67–77]	72 [66–76]	0.573
Body mass index	kg/m^2	26.5 [24.3–29.4]	26.7 [24.4–29.4]	25.5 [24.3–29.4]	0.544
CHA_2DS_2Vasc		3 [2–4]	3 [2–4]	3 [1–5]	0.622
Duration of AF	months	3 [2–4]	3 [2–4]	2 [1.3–3]	0.300
Peak left atrial strain	%	18.6 ± 8.1	18.8 ± 7.9	17.7 ± 10.2	0.641
Atrial dyssynchrony (TP-SD)	%	12.8 [7.7–20.3]	12.9 [7.3–20.2]	11.2 [8.4–23.2]	0.941
Atrial dyssynchrony (TP-SD)/strain ratio		0.69 [0.37–1.35]	0.68 [0.37–1.36]	0.80 [0.38–1.36]	0.728
Left atrial volume	ml/m^2	33 [25–46]	37 [29–46]	42 [25–55]	0.513
Left ventricular longitudinal systolic strain	%	−15.2 [−17.8 to −12.7]	−15.3 [−17.9 to −13.3]	−12.1 [−17.5 to −10.3]	0.191
Left ventricular diastolic volume	ml/m^2	46 [38–58]	45 [37–56]	50 [41–57]	0.203
Left ventricular ejection fraction	%	55 [48–60]	55 [49–60]	50 [39–60]	0.222
Left ventricular mass	g/m^2	104 [69–147]	100 [67–144]	122 [84–202]	0.078
Mitral deceleration time	ms	220 [183–254]	220 [183–254]	210 [176–239]	0.378
Amiodarone	%;*n*	100;61	48;54	47;7	1.00
Digitalis	%;*n*	100;47	36;41	40;6	1.00
Beta-blockers/sotalol	%;*n*	100;61	45;51	67;10	1.00
Propafenone/Flecainide	%;*n*	100;21	14;16	33;5	1.00
Calcium channel blockers	%;*n*	100;12	9;10	13;2	1.00
ACE-inhibitors/AT-1 receptor blockers	%;*n*	100;83	66;75	53;8	1.00

AF, atrial fibrillation; CHA_2DS_2Vasc, congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–75 years, sex category [female]; ACE, angiotensin-converting enzyme; AT, angiotensin; TP-SD, time-to-peak standard deviation.
[a] Sinus rhythm vs. AF recurrence.

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Table 5
Variables in the patients followed-up after electrical cardioversion ($n = 128$) divided according to quartiles of non-invasively-computed atrial stiffness (*computed*-K_{la}).

		1st quartile ($n = 32$)	2nd quartile ($n = 32$)	3rd quartile ($n = 32$)	4th quartile ($n = 32$)	p
Computed atrial stiffness (*computed*-K_{la})	mmHg/mm^2	0.57 [0.48–0.64]	0.82 [0.74–0.88]	1.05 [0.95–1.13]	1.66 [1.41–2.31]	<0.001
Peak left atrial strain	%	20.80± 9.22	21.59± 7.05	16.46± 5.89	15.71± 8.56	0.004
Atrial dyssynchrony (TP-SD)	%	11.61 [8.02–23.72]	10.79 [6.62–16.05]	15.54 [5.95–23.44]	13.58 [7.88–21.52]	0.567
Atrial dyssynchrony (TP-SD)/strain ratio		0.57 [0.31–1.28]	0.58 [0.35–0.91]	1.00 [0.41–1.53]	1.07 [0.53–1.69]	0.039
Left atrial volume	ml/m^2	37.1 [28.4–47.5]	33.7 [25.9–45.3]	37.9 [30.7–47.5]	36.8 [26.2–50.9]	0.796
Mitral deceleration time	ms	220 [188–262]	222 [180–255]	221 [203–254]	199 [156–237]	0.08
Left ventricular stiffness (K_{lv})	mmHg/ml/m^2	0.12 [0.08–0.17]	0.11 [0.08–0.16]	0.10 [0.07–0.12]	0.14 [0.09–0.22]	0.017
Computed atrial stiffness (*computed*-K_{la}) +left ventricular stiffness (K_{lv})	mmHg/ml/m^2	0.78 [0.69–0.88]	1.03 [0.94–1.11]	1.27 [1.13–1.34]	1.98 [1.76–2.87]	<0.001
Age	years	75.0 [66.0–79.3]	71.0 [65.8–77.0]	74.0 [67.5–77.0]	73.0 [67.0–76.0]	0.787
CHA_2DS_2Vasc		3.0 [2.0–4.0]	3.0 [2.0–3.3]	4.0 [2.0–5.0]	3.0 [2.0–4.0]	0.189
Body mass index	kg/m^2	25.7 [23.4–29.2]	26.6 [24.1–29.0]	27.7 [25.3–31.6]	26.0 [24.4–29.4]	0.372
Atrial fibrillation recurrence	%;*n*	9;3	9;3	3;1	25;8	0.09

K_{la}, atrial stiffness; K_{lv}, ventricular stiffness; TP-SD, time-to-peak standard deviation; CHA_2DS_2Vasc, congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–75 years, sex category [female].

piston-like movement of the shared mitral annulus and the adjacent ventricle. According to the "constant volume heart" physiological concept, in fact, the source of LA longitudinal deformation is the ventricle doing external work on the atrium, as the ventricular cavity ejects blood into the aorta and then fills through the open mitral valve [19]. Accordingly, it has been shown in a large population of acutely infarcted patients, that the prognostic value of LA peak strain, taken as a representative of the cavity reservoir function, is dependent on LV longitudinal function, besides LA size [20].

However, passive LA cavity properties, on which the LV is also doing work, do also contribute to the relationship [19]. In our study the longitudinal deformation of the contracting ventricle modulated K_{la} (Fig. 3). Stiffness is conventionally defined as the force required to displace a passive spring by a unit length. Such formulation, which incorporates the deformation/strain concept (definition is change in length per unit length), describes the mechanical characteristics of the LA cavity and, potentially, the extent to which they are affected by fibrosis, known to be predictive of AF recurrence in the short- and long-term [21–23].

Clinical relevance of LA stiffness (K_{la})

In patients undergoing catheter ablation for AF, the stiff LA syndrome has been reported [24]. In a series of 1380 consecutive patients stiff LA syndrome was detected in 19 subjects after AF ablation. In a multivariate logistic model, severe LA scarring, as evaluated using voltage mapping, predicted the development of stiff LA syndrome [25]. Atrial dilation is an important finding in this syndrome, but the increased chamber stiffness is more important [26]. In our study, LA stiffness was not related to LA volume.

The reciprocation between the atrium and the ventricle would caution against the possibility of non-invasively detecting stiffening of the atrium using strain only [19,27]. In our prospective population, however, we were able to demonstrate that patients who were in the highest *computed*-K_{la} quartile (*computed*-K_{la} derived from LV longitudinal strain according to the formula obtained from the invasive study), tended to have the highest incidence of AF recurrences as compared with the remaining 3 quartiles (Table 5). The TP-SD/LA peak strain ratio also increased along with quartiles, with a behavior that mirrored the one depicted by this index in the invasive study, where patients were grouped according to increasing tertiles of mean LA pressure (Fig. 2, right), suggesting that temporal and mechanical inhomogeneities occur within the atrial wall along with increasing degrees of mean LA pressure.

These data suggest that LV longitudinal strain modulates to a various extent LA function and stiffness and that such modulation may influence predictability of AF relapses in patients reverted to sinus rhythm 1 month before, as our prospective cohort suggests. Only the combination of atrio-ventricular stiffness (*computed*-K_{la} +$_{lv}$), and not K_{la} alone, however, appears to have the potential for predicting AF recurrences in the short-term after cardioversion with reasonable sensitivity and specificity. This is in line with the notion that impaired LV longitudinal strain is a novel powerful imaging biomarker capable of identifying patients at high cardiovascular risk, even in the presence of a preserved EF [28,29] and with the recent proposal of a plausible connection between LV characteristics and an increased likelihood of atrial arrhythmia recurrence in patients who had undergone previous AF catheter ablation [30,31].

Limitations

A fluid-filled catheter system was used to estimate LA pressure, but this monitoring system had been previously tested relative to a micromanometer-tipped catheter. A time-correction factor for the LA pressure tracing was used in the present study.

The mean K_{la} values (1.11 mmHg/ml for pressures between 5.6 mmHg and 13.3 mmHg and 1.53 mmHg/ml for pressures between 14.3 mmHg and 20.4 mmHg) are comparable with the literature where the mean K_{la} was assessed during open-heart surgery (0.48 mmHg/ml for pressures between 5.1 mmHg and 13.3 mmHg and 0.76 mmHg/ml for pressures between 13.6 mmHg and 20.6 mmHg) [5], with the notion that K_{la} is known to decrease with pericardiectomy.

The estimation of K_{la} and K_{lv} in the present study was not pressure-independent and this might have had an impact on our results. Finally, the number of patients in our invasive study was relatively small ($n = 20$). Our findings, however, are consistent with a published larger study ($n = 155$) on LA stiffness and its relation with diastolic dysfunction, in which authors demonstrated that LA stiffness index was an independent predictor of recurrence of AF after AF ablation [32].

In the invasive protocol 13 patients were in AF and only 7 in sinus rhythm. This might have had an impact on the quality of acquired data. We are convinced, however, that the averaging process adopted on selected not necessarily consecutive beats, further interpolated to a fixed number of time-sampling points, should have been adequate to minimize potential problems deriving from rhythm inhomogeneities.

In the prospective patients' population echocardiograms were acquired 1 month after cardioversion only in patients in sinus rhythm. We have to acknowledge that this study design may limit the clinical implications of our findings because we excluded

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patients who experienced very early AF episodes after cardioversion and we could not predict AF recurrences ahead of the procedure.

Conclusion

K_{la} can be assessed invasively in patients undergoing AF ablation and it can be estimated non-invasively using LV longitudinal strain. Short-term (5 months) AF recurrence after cardioversion tends to be more frequent in the highest quartile of computed left atrial stiffness (*computed-*K_{la}). However, only when combined with ventricular stiffness (K_{lv}), *computed-*K_{la} can anticipate recurrences in a population of persistent AF patients.

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Disclosures

The authors declare that there is no conflict of interest.

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