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Clinical Research

Characterization of left atrial strain in left ventricular hypertrophy: A study of Fabry disease, sarcomeric hypertrophic cardiomyopathy and cardiac amyloidosis☆

Charles Massie[a,b,c,1,*], Frédérique Dubé[a,b,d], Soumaya Sridi-Cheniti[a,b], Julien Ternacle[a,b,e], Stéphane Lafitte[a,b,e], Patricia Réant[a,b,e,f]

[a] *Bordeaux University Hospital, 33000 Bordeaux, France*
[b] *University of Bordeaux, 33000 Bordeaux, France*
[c] *Hôpital Sacré-Cœur de Montréal, Montreal, QC H4J 1C5, Canada*
[d] *Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC J1J 3H5, Canada*
[e] *CIC-P 1401, 33600 Bordeaux-Pessac, France*
[f] *Inserm 1045, 33600 Pessac, France*

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ABSTRACT

Background: Patients with left ventricular hypertrophy (LVH) often maintain preserved left ventricular ejection fraction in the early stages of the disease. There is a need to identify simple and reliable variables beyond left ventricular ejection fraction to recognize those at risk of developing adverse clinical outcomes.
Aims: To examine left atrial (LA) strain in patients with hypertrophic cardiomyopathy (HCM), cardiac amyloidosis (CA) and Fabry disease (FD), pathologies known to cause LVH, and the relationship between LA strain and adverse clinical outcomes.
Methods: In this retrospective cohort study, LA strain was measured and compared among patients with HCM, CA and FD. Relationships between LA and left ventricular strain, and LA strain and adverse cardiovascular events were evaluated. The primary outcome was first occurrence of cardiovascular mortality, device implantation, heart failure hospitalization, new-onset atrial fibrillation or stroke.
Results: A total of 191 patients were included (24 with FD, 87 with HCM, 80 with CA). LA reservoir strain was highest in patients with HCM (26%, interquartile range [IQR] 20%, 32%), followed by those with FD (20.5%, IQR: 14%, 27.8%) and CA (11%, IQR: 7%, 18.8%) ($P < 0.001$). LA strain correlated well with left ventricular strain in patients with LVH, with CA showing the best correlation ($r = -0.70$, 95% confidence interval [95% CI]: −0.80 to −0.56; $P < 0.001$). Multivariable Cox regression analysis showed that LA reservoir strain was significantly associated with the primary outcome in all patients (hazard ratio: 0.91, 95% CI: 0.84 to 0.99; $P = 0.03$) and in those with CA (hazard ratio: 0.90, 95% CI: 0.82 to 0.99; $P = 0.023$).
Conclusions: LA strain was more reduced in CA than in FD and HCM, probably as a result of atrial wall infiltration, and was associated with adverse clinical outcomes in our heterogenous LVH population and patients with CA.

1. Abbreviations

ATTR NYD	cardiac amyloidosis, subtype not yet determined
ATTRv	mutant/variant transthyretin cardiac amyloidosis
ATTRwt	wild-type transthyretin cardiac amyloidosis
BNP	brain natriuretic peptide
CA	cardiac amyloidosis
CI	confidence interval

☆ X post (Tweet): Left atrial strain is a key marker of adverse outcomes in LVH. A study of 191 patients shows that LA strain is most reduced in cardiac amyloidosis vs. hypertrophic cardiomyopathy and Fabry disease and correlates with adverse clinical outcomes. #Cardiology #LVH #Research.

* Corresponding author at: Hôpital Cardiologique Haut-Lévêque, avenue de Magellan, 33604 Pessac, France.
E-mail address: charles.massie@umontreal.ca (C. Massie).
[1] X (Twitter) handle: @DrCharlesMassie, @TernacleJ, @stelafitte.

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FD	Fabry disease
GLS	global longitudinal strain
HCM	hypertrophic cardiomyopathy
LA	left atrial
LGE	late gadolinium enhancement
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
TTE	transthoracic echocardiography

2. Background

Left ventricular hypertrophy (LVH) can be caused by a wide range of pathologies, including hypertensive, infiltrative and genetic diseases. Patients with LVH often maintain preserved left ventricular ejection fraction (LVEF) in the early stages of the disease. There is a need to identify simple and reliable variables beyond LVEF to recognize those at risk of developing adverse clinical outcomes. Left atrial (LA) strain adequately grades diastolic function and filling pressures, and can identify patients at risk of developing atrial fibrillation [1–3]. While determinants of LA strain include left ventricular (LV) strain and LA/LV volume ratio, LA strain carries prognostic significance beyond LV strain in diverse cardiac conditions [4].

Increased LV wall thickness in sarcomeric hypertrophic cardiomyopathy (HCM) and Fabry disease (FD) results from myocyte hypertrophy, whereas cardiac amyloidosis (CA) stems from amyloid protein deposition in the extracellular space. In FD, sphingolipid accumulation within the myocytes is responsible for their hypertrophy. Despite differing pathophysiology, these diseases can present with unexplained LVH and similar clinical complications, such as stroke, atrial fibrillation, conduction disease and heart failure. LA strain has been studied individually and in pairs in these pathologies [5–9], but has yet to be characterized in a population comprised of HCM, CA and FD in a single combined analysis.

This study aimed to: (1) compare LA strain between HCM, CA and FD; and (2) explore the association between LA strain and clinical outcomes in this population.

We hypothesized that LA strain is significantly more reduced in patients with CA and FD compared with HCM (caused by amyloid and sphingolipid infiltration, respectively) and that LA strain is associated with clinical outcomes in this population of patients with LVH.

3. Methods

We conducted a single-centre retrospective observational cohort study. Patient enrolment was done locally at the Hereditary Cardiomyopathy Reference Centre, a division of Bordeaux University Hospital, France (ClinicalTrial.gov identifier: NCT02559726). The centre cares for patients with LVH of different aetiologies, by performing genetic testing as well as providing echocardiographic and clinical follow-up.

3.1. Inclusion criteria and definitions

Eligible individuals were patients aged ≥ 18 years with either FD, sarcomeric HCM (obstructive and non-obstructive) or CA. Patients were evaluated and followed in our LVH clinic between 2014 and 2023.

Echocardiographic LVH was defined as: LV mass index > 115 g/m^2 in men and > 95 g/m^2 in women (using the linear method) or septal or posterior wall thickness > 10 mm in men and 9 mm in women with a previous genetic diagnosis of HCM, CA or FD (as measured by transthoracic echocardiography [TTE] in parasternal long-axis view, at end-diastole).

The diagnosis of FD was based on genetic testing with mutation identification. The diagnosis of HCM was based on consensus criteria [10] (non-dilated left ventricle with a maximal wall thickness ≥ 15 mm not explained by other cardiac or systemic conditions), and corroborated by genetic testing or family history. The diagnosis of CA was based on genetic testing with mutation identification in hereditary CA (ATTRv) and scintigraphy with bone tracers in wild-type CA (ATTRwt). The diagnosis of light-chain amyloidosis was based on serum free light-chain quantification and ratio as well as bone marrow biopsies, combined with either imaging evidence of cardiac involvement or myocardial biopsy.

3.2. Exclusion criteria

Patients were excluded if they met any of the following criteria: image quality not allowing for LA strain measurement; and conditions that may alter LA and LV strain individually and their interaction (i.e. more-than-moderate mitral regurgitation, more-than-moderate aortic regurgitation, previous surgery for valvular heart disease, atrial fibrillation during baseline TTE, history of atrial fibrillation ablation, device-mediated stimulation and previous septal reduction therapy).

3.3. TTE

All patients underwent resting TTE examinations using Vivid E95 or E9 ultrasound machines (GE Healthcare, Chicago, IL, USA). Ultrasound recordings were done using standardized views, with two-dimensional frame rates exceeding 50 Hz. The different modalities included pulsed, continuous and colour wave Doppler, with the recorded data being stored for subsequent analysis on an external workstation (EchoPAC®, version 203; GE Healthcare, Chicago, IL, USA). Focus was put on the LV outflow tract to exclude systolic anterior motion of the mitral valve. Continuous wave Doppler in the LV outflow tract was used to identify blood flow acceleration and quantify maximal outflow velocity. Pulsed wave tissue Doppler imaging was performed in the apical four-chamber view, focusing on lateral and septal portions of the mitral annulus, as well as the lateral tricuspid annulus. Estimation of LV peak systolic global longitudinal strain (GLS) was done using a two-dimensional speckle tracking method (17-segment model) across the three apical views, as per current recommendations [11]. Echocardiographic evaluation was performed by experienced cardiologists in accordance with published guidelines from the American Society of Echocardiography [12].

3.4. LA strain measurement

The three phases of LA function are reservoir, conduit and contraction phases. LA strain curves depict an initial positive peak at end-systole (reservoir), followed by two descending phases in early diastole (passive emptying or conduit) and late diastole (active emptying or contraction). LA strain was measured retrospectively using EchoPAC's dedicated LA speckle tracking software. Measurements were performed by two experienced echocardiographers (C. M. and F. D.) by manually positioning three points (two at the mitral annulus and one at the uppermost point of the left atrium) with automatic wall contouring in both the apical four- and two-chamber views. Tracking of the LA wall was considered inadequate if the software's tracking markers did not accurately follow the motion of the LA wall (determined qualitatively) (Fig. 1). The echocardiographers were blinded to clinical data at the time of LA strain measurement.

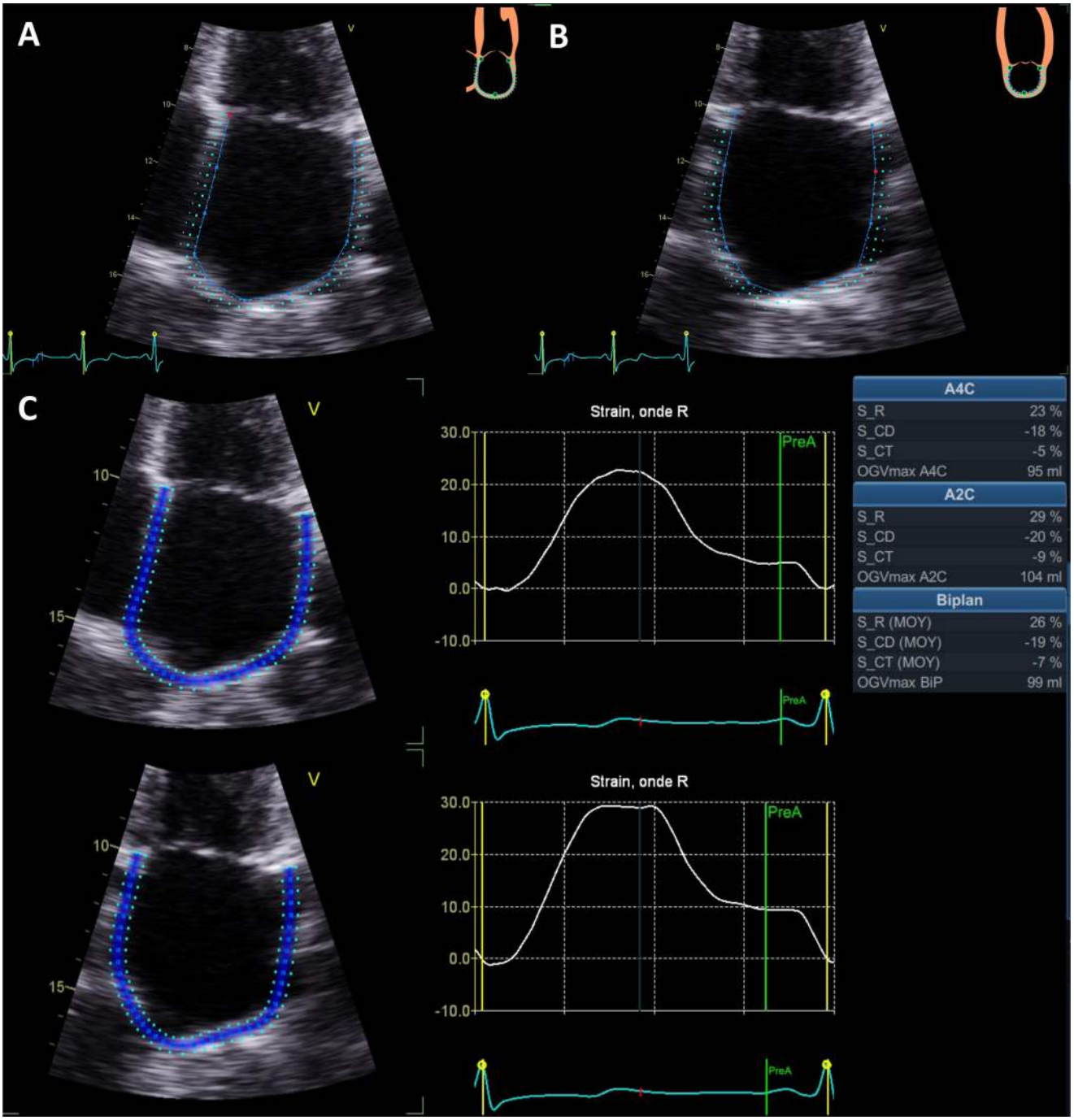


Fig. 1. A–B. Example of left atrial strain (LA) measurement in a patient with Fabry disease. Measurement is done by manually positioning three points (two at the mitral annulus and one at the lowest point of the LA wall) with automatic wall contouring in the four-chamber (A) and two-chamber (B) views. C. Software-generated values of S_R (reservoir or peak systolic strain), S_CD (conduit or early diastolic strain), S_CT (contraction or late diastolic strain) and OGV_{max} (maximal LA volume) in four-chamber (A4C), two-chamber (A2C), and biplane (Biplan; BIP) views were obtained and displayed. MOY: mean.

3.5. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed on 129 participants (68%) using a 1.5 Tesla scanner (Magnetom Avanto; Siemens, Munich, Germany). The scans included localized images (axial, coronal, sagittal planes), cine images, native T1 mapping and late gadolinium enhancement (LGE) imaging and postcontrast T1 mapping. Cine images of the left ventricle were acquired in four-, three- and two-chamber views, plus short-axis views, using breath-hold and gated sequences. LV volumes, mass and ejection fraction using the modified Simpson's rule were calculated from short-axis cine images. LGE imaging was captured 10–12 minutes after administration of gadoterate meglumine contrast agent, and LGE patterns were assessed qualitatively.

Regarding T1 mapping, images were acquired both before and after the administration of contrast, using the MOdified Look Locker Inversion-recovery (MOLLI) sequence. To derive myocardial T1 values, regions of interest were manually delineated in the septal region at the midventricular level, avoiding regions of LGE.

3.6. Consent

The study adhered to the principles outlined in the Declaration of Helsinki, and received approval from the Institutional Review Board or Independent Ethics Committee of our centre. The authors had unrestricted access to the study data, and assume responsibility for the accuracy and reliability of this report. Patients were included after providing informed consent.

3.7. Clinical outcomes

The primary clinical outcome was a composite outcome of first occurrence of cardiovascular mortality, new device implantation (either pacemaker or defibrillator), new heart failure hospitalization, new-onset atrial fibrillation or new ischaemic stroke. Clinical data and outcomes were collected retrospectively from chart review and patients' clinical follow-up. Clinical events occurring in other healthcare centres were systematically reported to our centre and incorporated into the analyses.

3.8. Interobserver and intraobserver variability

Thirty cases were selected at random for reproducibility analyses. Half were initially measured by one operator and the other half by a second operator (both experienced echocardiographers). Each case was reanalysed by the same initial operator a few months later for assessment of intraobserver variability, and cases measured by one operator were reanalysed by the other operator for assessment of interobserver variability. Each operator was blinded to previous LA strain measurements.

3.9. Statistical analysis

Baseline, clinical, paraclinical and procedural characteristics are expressed as means ± standard deviations for continuous variables or as counts with percentages for categorical variables, as appropriate. Comparison of these variables between groups was performed using analysis of variance (ANOVA) or Pearson's χ^2 test, respectively. Normality of the variables was tested using the Shapiro–Wilk test. Non-parametric variables are expressed as medians (interquartile ranges) and were compared using the Kruskal–Wallis H test. Correlation between LA and LV strains was assessed using Pearson correlation coefficients and is presented in scatter plots.

Cox univariate and multivariable proportional hazards regression models were used to identify variables associated with the clinical outcome. These variables, which included echocardiographic, clinical and biochemical factors, were selected for their known prognostic value in cardiac disease. Variables with the strongest statistically significant association with the primary outcome in univariate analysis were used to create the multivariable model, with the number of events per group dictating the number of variables per model. Finally, we performed a Kaplan–Meier analysis to evaluate occurrence of the primary outcome over time, as stratified by the aetiology of LVH.

Inter- and intraobserver variabilities were assessed using the intraclass correlation coefficient and coefficient of variation. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, NY, USA). A two-tailed *P*-value < 0.05 was considered statistically significant.

4. Results

A total of 494 patients were screened at Bordeaux University Hospital, and 248 patients were excluded as their images were inadequate for retrospective biplane LA strain processing. Other causes of exclusion were significant valve disease, previous septal reduction therapy or atrial arrythmia during the index TTE. A total of 191 patients were included in the study: 24 with FD; 87 with HCM; and 80 with CA (Fig. A.1).

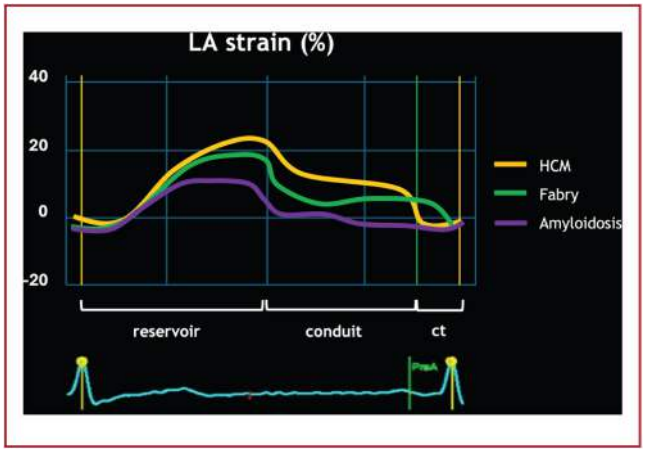


Fig. 2. Example of left trial (LA) strain curves in different left ventricular hypertrophy subgroups. The three phases of LA function are reservoir, conduit and contraction (ct) phases. Preatrial contraction (PreA) precedes the atrial kick. HCM: hypertrophic cardiomyopathy.

4.1. Baseline clinical and echocardiographic characteristics

Patients with CA were older, with a mean age of 77 years, and were mostly men; they had higher brain natriuretic peptide (BNP) concentrations and had previous atrial fibrillation episodes and heart failure hospitalizations more frequently than other groups (Table 1). Most patients with HCM were non-obstructive (68% vs. 32%) (Table A.1), asymptomatic (70% in New York Heart Association class I) and had low BNP concentrations. Patients with FD had more previous episodes of stroke at baseline.

In patients with CA versus other groups, LVEF was lower, LV GLS was more altered (more positive) and systolic pulmonary artery pressure, E/E' and E/A ratios were higher. Patients with CA had > mild MR more often than other groups. In patients with HCM, the interventricular septum was thicker, which led to a smaller LV systolic cavity (lower LV end-systolic volume). By contrast, patients with FD had a less thick interventricular septum and a lower maximal wall thickness (by TTE and magnetic resonance imaging), but thicker posterior walls (14.9 ± 3.4 mm); they also had a higher LA volume. Patients with CA had higher T1 values on magnetic resonance imaging, and tended to have more LGE, albeit not statistically significant (Table 2).

4.2. Characterization of LA strain in different subgroups

LA reservoir strain (biplane and single-plane four-chamber view) was significantly higher in patients with HCM, followed by FD and CA: 26% (20%, 32%), 20.5% (14%, 27.8%) and 11% (7%, 18.8%), respectively ($P < 0.001$). The differences between all these groups were statistically significant. All components of LA strain were significantly more reduced in patients with CA versus HCM and in patients with CA versus FD (Table 3, Fig. 2).

There was no statistically significant difference in LA strain between obstructive and non-obstructive HCM. LA reservoir strain (biplane and two-chamber view) and conduit strain were significantly lower in patients with ATTRwt versus ATTRv. There was a trend for lower LA strain in patients with light-chain amyloidosis versus ATTRv, but this was not statistically significant (Table A.2).

Table 1
Baseline clinical characteristics.

	FD ($n=24$)	HCM ($n=87$)	CA ($n=80$)	All LVH[a] ($n=191$)	P[b]
Age (years)	62.5 ± 9.8	61.2 ± 14.8	77.2 ± 10.1	68.1 ± 14.6	<0.001
Males	13 (54)	61 (70)	64 (80)	138 (72)	0.039
BSA	1.77 ± 0.15	1.89 ± 0.21	1.83 ± 0.18	1.84 ± 0.20	<0.001
NYHA class					<0.001
I	8 (35)	57 (70)	16 (23)	81(46)	
II	14 (61)	22 (26)	50 (71)	86 (49)	
III	1 (4)	3 (4)	4 (6)	8 (5)	
BNP (pg/mL)	102 (49, 222)	58 (33, 150)	199 (112, 408)	108 (49, 222)	<0.001
History of AF	1 (4.2)	11 (12.6)	21 (26.3)	33 (17)	0.013
History of stroke	5 (21)	4 (4.6)	4 (5)	13 (7)	0.014
History of HF hospitalization	0 (0)	0 (0)	12 (15)	12 (6)	<0.001

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). AF: atrial fibrillation; BNP: brain natriuretic peptide; BSA: body surface area; CA: cardiac amyloidosis; FD: Fabry disease; HCM: hypertrophic cardiomyopathy; HF: heart failure; LVH: left ventricular hypertrophy; NYHA: New York Heart Association.
[a] Comprises patients with FD, HCM and CA.
[b] Comparison between LVH groups (FD, HCM, CA).

Table 2
Standard echocardiographic, Doppler and magnetic resonance imaging data in patients with left ventricular hypertrophy of different aetiologies.

	FD ($n=24$)	HCM ($n=87$)	CA ($n=80$)	All LVH[a] ($n=191$)	P[b]
LV GLS (%)	−15.3 ± 4.7	−16.9 ± 4.0	−13.7 ± 3.6	−15.4 ± 4.2	<0.001
LVEF (%)	64.5 ± 11.4	68.7 ± 6.3	59.1 ± 10.5	64.1 ± 10.0	<0.001
LVEDV (mL)	94.9 ± 28.8	81.2 ± 26.3	85.1 ± 26.2	84.7 ± 26.8	0.09
LVESV (mL)	39 (28, 49)	26 (19, 34)	29 (25, 35)	28 (21, 39)	<0.001
Maximum wall thickness (mm)	15 (13, 16)	17 (15, 18)	16 (14, 17)	16 (14, 18)	0.030
IVS (mm)	13.8 ± 3.1	16.6 ± 4.0	15.4 ± 2.6	15.7 ± 3.4	<0.001
PW (mm)	14.2 ± 3.8	10.0 ± 2.4	13.0 ± 2.5	12.0 ± 3.1	<0.001
LV mass index (g/m^2)	132 (114, 174)	116 (90, 147)	135 (114, 153)	123 (102, 153)	0.005
LA volume (mL/m^2)	44.0 ± 13.1	35.0 ± 14.4	42.1 ± 13.4	39.1 ± 14.3	<0.001
LVEDD (mm)	45.7 ± 5.3	44.4 ± 6.6	43.6 ± 5.3	44.2 ± 5.8	0.31
E/E′	12.4 ± 4.4	9.9 ± 3.7	13.8 ± 5.8	11.9 ± 5.1	<0.001
E/A	0.9 (0.8, 1.2)	1.0 (0.7, 1.4)	1.4 (0.8, 2.7)	1.1 (0.8, 1.6)	0.06
Systolic PAP (mmHg)	29.2 ± 5.9	27.6 ± 7.0	32.8 ± 10.0	30.5 ± 8.8	0.003
S′ (cm/s)	12.0 ± 2.0	13.4 ± 2.2	12.0 ± 3.2	12.6 ± 2.7	0.003
AR grade					0.14
None	17 (71)	77 (89)	67 (84)	161 (84)	–
Mild	6 (25)	7 (8)	8 (10)	21 (11)	–
Mild to moderate	0 (0)	1 (1)	4 (5)	5 (3)	–
Moderate	1 (4)	2 (2)	1 (1)	4 (2)	–
MR grade					<0.001
None	4 (17)	40 (46)	13 (16)	57 (30)	–
Mild	13 (54)	36 (41)	16 (20)	65 (34)	–
Mild to moderate	0	0 (0)	36 (45)	36 (19)	–
Moderate	7 (29)	11 (13)	15 (19)	33 (17)	–
MRI data					
Maximum wall thickness (mm)	15.4 ± 4.5	17.8 ± 3.4	16.0 ± 4.7	17.0 ± 4.1	0.019
T1 mapping	883 ± 74	1032 ± 83	1112 ± 63	1031 ± 120	<0.001
Presence of fibrosis	14 (70)	51 (69)	28 (82)	93 (72)	0.33

Data are expressed as mean ± standard deviation, median (interquartile range) or number (%). AR: aortic regurgitation; CA: cardiac amyloidosis; FD: Fabry disease; GLS: global longitudinal strain; HCM: hypertrophic cardiomyopathy; IVS: interventricular septum; LA: left atrial; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVH: left ventricular hypertrophy; MR: mitral regurgitation; MRI: magnetic resonance imaging; PAP: pulmonary artery pressure; PW: posterior wall; S′: lateral tricuspid annulus peak systolic velocity.
[a] Comprises patients with FD, HCM and CA.
[b] Comparison between LVH groups (FD, HCM, CA).

4.3. Correlation between LA strain and LV GLS

LA reservoir strain showed good correlation with LV GLS in our population of patients with LVH ($r=-0.63$, 95% confidence interval [95% CI]: −0.71 to −0.54; $P<0.001$) (Table 4, Fig. A.2). LA strain had a better correlation with LV GLS in patients with CA versus other groups ($r=-0.70$, 95% CI: −0.80 to −0.56; $P<0.001$) (Table 4, Fig. 3). For the same LV GLS values, patients with CA had lower LA strain values, followed by patients with FD then those with HCM (Fig. 3).

4.4. Association with adverse clinical outcomes

During the median follow-up period of 22 months (7, 55 months), we recorded 66 clinical outcome events (Table 5). Patients with FD developed the composite primary outcome relatively more often, and had a significantly higher number of events per patient than those with CA or HCM (respectively, 1.21 ± 1.2 vs. 0.46 ± 0.75 vs. 0.38 ± 0.69; $P<0.001$) (Table 5, Fig. A.3).

Table 3
Left atrial strain in patients with left ventricular hypertrophy of different aetiologies.

	FD (n = 24)	HCM (n = 87)	CA (n = 80)	All LVH (n = 191)	P[a]
LA reservoir strain, four-chamber view	19 (13.3, 22.8)	25 (19, 30)	10 (7, 17.5)	19 (10, 25)	<0.001
LA reservoir strain, two-chamber view	21.5 (13.3, 30)[b]	26 (20, 33)[b]	12 (7.3, 20.8)	21 (12, 28)	<0.001
LA reservoir strain, biplane	20.5 (14, 27.8)	26 (20, 32)	11 (7, 18.8)	20 (11, 26)	<0.001
LA conduit strain	−11 (−15, −7)	−13 (−18, −9)	−7 (−9.8, −5)	−10 (−15, −6)	<0.001
LA contraction strain	−9 (−12.8, −4.5)[b]	−11 (−15, −7)[b]	−3 (−8.8, −0.3)	−8 (−12, −3)	<0.001

Data are expressed as median (interquartile range). CA: cardiac amyloidosis; FD: Fabry disease; HCM: hypertrophic cardiomyopathy; LA: left atrial; LVH: left ventricular hypertrophy.
[a] Comparison between all LVH subgroups (FD, HCM, CA).
[b] Comparisons between these groups were not statistically significant (P > 0.05); all other comparisons between subgroups were statistically significant (P < 0.05).

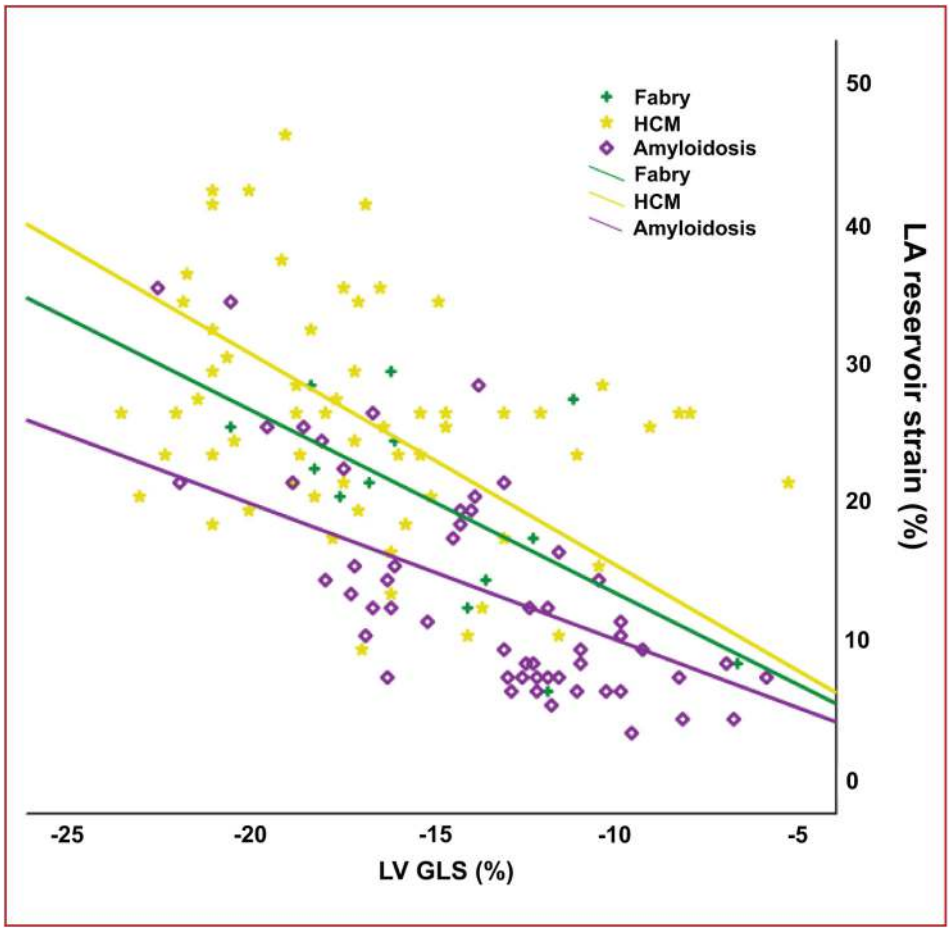


Fig. 3. Scatter plot displaying correlation between left atrial (LA) reservoir strain (biplane) and left ventricular (LV) global longitudinal strain (GLS) in different patient subgroups with left ventricular hypertrophy. HCM: hypertrophic cardiomyopathy.

In univariate Cox regression analysis, LA reservoir strain (biplane) was the factor most associated with the primary composite outcome in all patients with LVH. Other associated factors were LVEF, BNP concentration, LV GLS, LA volume, LV mass index, New York Heart Association class and E/E′ mean (Table A.3). LA reservoir strain was associated with the primary outcome in HCM and CA (P < 0.05 for each), but not in FD (P = 0.38) (Table A.4).

In multivariable Cox regression analysis, and after adjusting for possible confounders, LA reservoir strain remained significantly associated with clinical outcome in all patients with LVH (hazard ratio: 0.91, 95% CI: 0.84 to 0.99; P = 0.03) and in the subgroup of patients with CA (hazard ratio: 0.90; 95% CI: 0.82 to 0.99; P = 0.023) (Table 6). In both groups, LVEF and LV GLS were not significantly associated with the primary outcome. Multivariable regression analysis was not performed for HCM and FD, as the absolute number of events in these subgroups was insufficient.

4.5. Interobserver and intraobserver variability

Analysis of inter- and intraobserver variability demonstrated very good to excellent reproducibility for all LA strain variables (Table A.5).

Table 4
Correlation between left atrial reservoir strain (biplane) and left ventricular global longitudinal strain.

	Correlation coefficient *r*	Count	95% CI	*P*
All LVH	−0.63	189	−0.71 to −0.54	<0.001
CA	−0.70	80	−0.80 to −0.56	<0.001
FD	−0.62	24	−0.82 to −0.29	0.001
HCM	−0.43	85	−0.59 to −0.24	<0.001

CA: cardiac amyloidosis; CI: confidence interval; FD: Fabry disease; HCM: hypertrophic cardiomyopathy; LVH: left ventricular hypertrophy.

5. Discussion

This study characterizes LA strain in a heterogenous population of patients with LVH, and its relationship with LV GLS, and confirms its clinical utility in such patients. To our knowledge, this is the first study on LA strain to include patients with FD, HCM and CA in a combined analysis. Key findings are: (1) LA reservoir strain (both biplane and single-plane apical four-chamber) is more reduced in CA versus FD and HCM; (2) LA reservoir strain is worse for the same LV GLS value in CA versus FD and HCM; and (3) LA reservoir strain is associated with adverse clinical events in our LVH population and in the CA subgroup.

5.1. FD

LA strain was significantly reduced in patients with LVH and a diagnosis of FD. Boyd et al. found reduced LA strain and increased LA volume in FD, even before the occurrence of LVH and initiation of enzyme therapy [13]. Pichette et al. showed that LA strain improves after adequate enzyme replacement therapy [14], supporting the idea that a primary atrial myopathy occurs early in the course of the disease, mediated in part by atrial sphingolipid accumulation [15,16], and is partially reversible.

Patients with FD had relatively more clinical events than other subgroups during follow-up (i.e. more strokes, heart failure hospitalizations and new-onset atrial fibrillation), highlighting the importance of early diagnosis and risk stratification in this known high-risk population.

Table 6
Multivariable Cox proportional hazards regression for primary outcome.

	HR	95% CI	Wald	*P*
All LVH				
LA reservoir strain	0.91	0.84 to 0.99	4.71	0.03
LVEF	0.95	0.89 to 1.01	3.21	0.07
BNP	1.00	1.000 to 1.003	4.34	0.04
LV GLS	0.94	0.76 to 1.15	0.375	0.54
LA volume	0.98	0.93 to1.04	0.50	0.48
LV mass index	1.01	0.99 to 1.02	0.99	0.32
CA				
LA reservoir strain	0.90	0.82 to 0.99	5.17	0.023
LVEF	0.96	0.90 to 1.02	1.70	0.19
LV GLS	1.04	0.84 to 1.28	0.10	0.75

BNP: brain natriuretic peptide; CA: cardiac amyloidosis; CI: confidence interval; GLS: global longitudinal strain; HR: hazard ratio; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

5.2. HCM

All phases of LA strain were reduced in patients with HCM, consistent with the findings of Popa-Fotea et al. [7]. We found that LA strain reduction in HCM and its correlation to LV strain was less pronounced than in FD and CA, suggesting less severe impairment in atrial mechanics in the HCM subgroup. We hypothesize that HCM's atrial dysfunction is passive and the result of increased LA pressure in a primarily ventricular pathology, rather than primary atrial involvement, as is believed to be the case in FD and CA. A comparison of 20 patients with FD and 20 with HCM in a 2018 report found no significant difference in atrial mechanics between the two pathologies, despite increased LA volume in HCM [8]. On the other hand, a cardiac magnetic resonance head-to-head comparison of atrial remodelling in HCM and FD found greater alteration in LA mechanics (increased volume, lower ejection fraction and lower reservoir and contractile functions) in patients with HCM for the same level of LVH [6]. These overall conflicting results may be due to different imaging modalities, varying levels of diastolic dysfunction and patient heterogeneity across studies.

5.3. CA

Our study includes the whole spectrum of CA, with most patients having ATTRwt, but also ATTRv and light-chain amyloidosis. All stages of LA strain were significantly reduced in CA, and LA strain

Table 5
Follow-up clinical data.

	FD (*n* = 24)	HCM (*n* = 87)	CA (*n* = 80)	All LVH[a] (*n* = 191)	*P*[b]
Follow-up (months)	55 (29, 71)	22 (13, 61)	13 (1, 27)	22 (7, 55)	–
All-cause death	4 (17)	0 (0)	1 (1.3)	5 (2.6)	<0.001
Sudden cardiac death	0 (0)	0 (0)	0 (0)	(0)	–
Myocardial infarction	1 (25)	0 (0)	0 (0)	1 (0.5)	–
Heart failure	1 (25)	0 (0)	1 (100)	2 (1)	–
Non-cardiac causes	2 (50)	0 (0)	0 (0)	2 (1)	–
Device implantation	7 (29)	18 (21)	15 (19)	40 (21)	0.54
Pacemaker	6 (86)	1 (6)	13 (87)	20 (10)	<0.001
ICD	1 (14)	17 (94)	2 (13)	20 (10)	<0.001
New HF hospitalization	4 (17)	4 (5)	3 (4)	11 (6)	0.048
New-onset AF	12 (50)	8 (9)	17 (21)	37 (19)	<0.001
New stroke	4 (17)	3 (3)	1 (1)	8 (4)	0.004
Composite primary outcome	15 (63)	24 (28)	27 (34)	66 (35)	0.006
Number of events per patient	1.21 ± 1.2	0.38 ± 0.69	0.46 ± 0.75	0.52 ± 0.83	<0.001

Data are expressed as median (interquartile range), number (%) or mean ± standard deviation. AF: atrial fibrillation; CA: cardiac amyloidosis; FD: Fabry disease; HCM: hypertrophic cardiomyopathy; HF: heart failure; ICD; implantable cardioverter-defibrillator; LVH: left ventricular hypertrophy.

[a] Comprises patients with FD, HCM and CA.

[b] Comparison between LVH groups (FD, HCM, CA).

reduction was more pronounced than in FD and HCM. This is consistent with studies comparing transthyretin CA with FD [5] and CA with hypertensive cardiomyopathy [9], showing greater LA strain reduction in CA compared with other cardiomyopathies. In addition to having more reduced absolute LA strain values, patients with CA had significantly worse LA reservoir strain for the same level of LV GLS compared with FD and HCM, which is a novel finding.

All in all, these findings are probably explained by a primary atrial myopathy in CA, secondary to amyloid infiltration of the LA wall [17]. Indeed, increased amyloid load was associated with worse LA strain and increased LA dysfunction by cardiac magnetic resonance [18]. CA is characterized by amyloid protein infiltration, not only in the LA, but in all cardiac chambers, with associated impairment in strain in all four cardiac cavities [19–21], LA strain being the most affected [19]. Considering that LA strain correlated well with LV GLS in our population, and that LV longitudinal strain is in part determined by the regional amyloid mass [22], we can infer that LA strain is a good indicator of the total amyloid burden of the LV and, by extension, the heart.

Finally, to explain the difference in LA function between CA and FD, both of which we suspect of having primary atrial involvement, we hypothesize that the extracellular infiltration of amyloid protein is either more detrimental to LA mechanics than the intracellular sphingolipid accumulation of FD, or that preferential amyloid infiltration of the LA occurs more in CA than sphingolipid accumulation in FD. Further research is needed to characterize the pathophysiological effects of these substances on LA function.

5.4. Association with adverse clinical events

In our heterogenous population of patients with LVH, LA strain showed the strongest association with adverse clinical events, even after adjusting for confounders such as LV GLS, LVEF and LV mass index. The association was similar to the one seen with BNP, a strong and well-established predictor of clinical events.

Whereas previous studies have linked LA strain with clinical events such as atrial fibrillation and stroke or functional status [14,23], LVEF was the only variable associated with our composite outcome in FD, with LA strain showing no significant association in univariate analysis. This lack of association might be explained by the small sample size, composite outcome design and the fact that LA strain might be less predictive of events such as heart failure hospitalization, device implantation or cardiovascular mortality in this complex multisystemic disease.

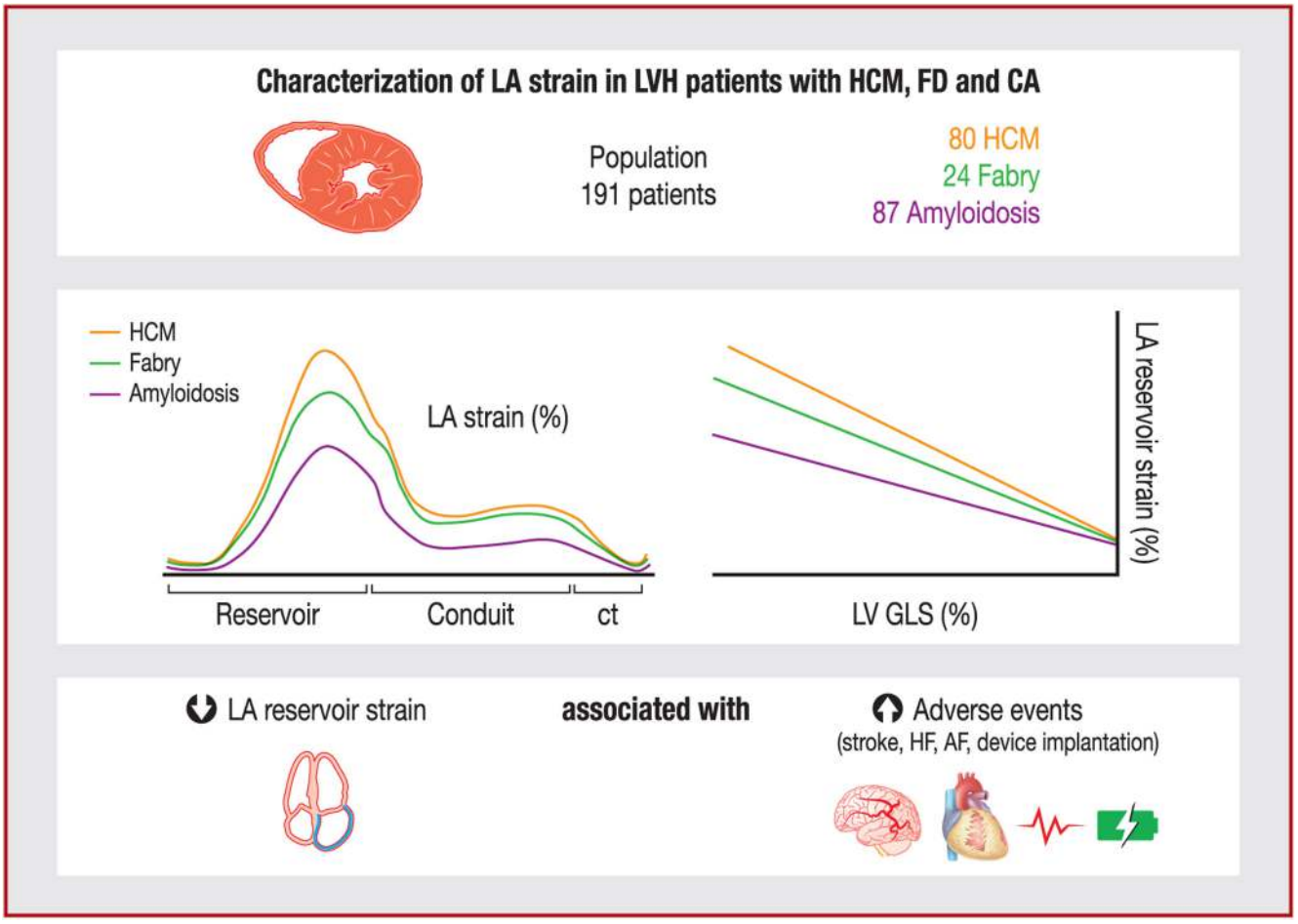
LA strain was significantly associated with the primary outcome in the CA subgroup after multivariable analysis, as opposed to LVEF and LV GLS. Previous reports have described the prognostic value of LA strain in CA, including its association with overall survival [24,25]. Our study shows that the strong association of LA strain with clinical events applies to a cohort comprised of different aetiologies of LVH, with different subtypes of CA. The prognostic strength of LA strain, which goes beyond LV GLS and LVEF, probably comes from its capacity to integrate disease progression in the form of cardiac infiltration or fibrosis, diastolic dysfunction and filling pressures, as well as clinical and biological factors [26]; it is an easy-to-use and reproducible tool that has become a necessary component of the routine echocardiographic evaluation of patients with LVH, especially those with preserved LVEF.

5.5. Study limitations

Our study needs to be considered in light of several limitations. First, it is a single-centre retrospective observational study, with the inherent biases of such a design. Patients in the different subgroups were not matched for disease severity; patients with CA were sicker, whereas those with HCM had less advanced disease. However, these real-world data are representative of the population with ATTRwt, affecting older co-morbid patients, whereas a large proportion of patients with HCM are diagnosed before phenotypic expression by familial genetic testing. Besides, LA strain remained associated with clinical events in multivariable analysis, even after adjusting for the degree of LVH (LV mass) and for disease severity (BNP). The low number of events in individual subgroups limited multivariable analyses in FD and HCM. Finally, the number of patients excluded for inadequate imaging was high, which may introduce a selection bias. This was a result of incomplete LA inclusion in either apical plane in non-dedicated studies, rather than difficulty in strain processing itself. In practice, single-plane four-chamber measurement is probably sufficient, which increases the feasibility of the analysis.

6. Conclusions

LA strain is more reduced in patients with CA compared with FD and HCM, probably as a result of a primary atrial myopathy. LA strain is strongly associated with adverse cardiovascular events in LVH and CA, is reproducible and should be part of the routine echocardiographic evaluation of LVH caused by FD, HCM or CA (Central Illustration).



Central Illustration. Left atrial (LA) strain in patients with left ventricular hypertrophy (LVH) with hypertrophic cardiomyopathy (HCM), Fabry disease (FD) and cardiac amyloidosis (CA). AF: atrial fibrillation; ct: contraction; GLS: global longitudinal strain; HF: heart failure; LV: left ventricular.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2024.12.013.

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