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Challenging the complementarity of different metrics of left atrial function: insight from a cardiomyopathy-based study

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Aims Left ventricular (LV) strain provides incremental values to LV ejection fraction (LVEF) in predicting outcome. We sought to investigate if similar relationship is observed between left atrial (LA) emptying fraction and LA strain.

Methods and results In this study, we selected 50 healthy subjects, 50 patients with dilated, 50 hypertrophic, and 50 infiltrative (light-chain (AL) amyloidosis) cardiomyopathy (CMP). Echocardiographic measures included LVEF and LA emptying fraction as well as LV and LA longitudinal strain (LVLS and LALS). After regression analysis, comparison of least square means of LA strain among aetiologies was performed. Intraclass correlation coefficient (ICC) and coefficient of variation (COV) were used in the assessment of variability and reproducibility of LV and LA metrics. The mean LVLS and all LA metrics were impaired in patients with all CMP compared with healthy subjects. In contrast to the moderate relationship between LVEF and LVLS ($r = -0.51$, $P < 0.001$), there was a strong linear relationship between LA emptying fraction and LA strain ($r = 0.87$, $P < 0.001$). In multiple regression analysis, total LA strain was associated with LVLS ($\beta = -0.48$, $P < 0.001$), lateral E/e′ ($\beta = -0.24$, $P < 0.001$), age ($\beta = -0.21$, $P < 0.001$), and heart rate ($\beta = -0.14$, $P = 0.02$). The least square mean of LA strain adjusted for the parameters was not different among aetiologies (ANOVA $P = 0.82$). The ICC (>0.77) and COV (<13) were acceptable.

Conclusion In contrast to LV measures, there is a strong linear relationship between volumetric and longitudinal deformation indices of left atrium irrespective of CMP aetiology. Either LA emptying fraction or LA strain could be used as an important parameter in predictive models.

Keywords strain imaging • left ventricular function • left atrial function

Introduction

Recently, there has been a great interest in strain (deformation) imaging of the left ventricle. One of the main interests in strain imaging is based on the fact that the changes in longitudinal deformation may occur prior to changes in ejection fraction (EF). For example, in patients with hypertrophic cardiomyopathy (HCM), left ventricular longitudinal strain (LVLS) is often impaired despite a preserved left ventricular ejection fraction (LVEF).[1–3]

Similar to the assessment of LV function, tissue Doppler imaging and speckle tracking techniques have been applied to left atrial (LA) deformation assessment and reported to be feasible.[4–7] These techniques allow non-invasive assessment of global as well as regional deformation of LA walls. In contrast to the LV architecture, left atrium consists of only two thin layers of myofibre: intermingling circumferential and longitudinal muscular bundles.[8,9] Therefore, it is unclear whether longitudinal LA strain provides additional information over and beyond LA emptying fraction. For this study, we

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hypothesized that LA strain would be closely related to LA emptying fraction in contrast to the relationship between LVEF and LVLS. If LA longitudinal strain and LA emptying fraction are closely related to each other, this could implicate that both metrics are unlikely to provide incremental for risk prediction or diagnostic value.

Therefore, the first objective of this study was to investigate the relationship between LA emptying fraction and LA strain in healthy controls as well as in patients with different types of cardiomyopathy [dilated cardiomyopathy (DCM), HCM, and light-chain (AL) amyloidosis (AMY)]. This relationship between LA emptying fraction and LA strain was compared with that between LVEF and LVLS. The second objective was to compare LA strain among different aetiologies after adjustments for differences in LVLS and E/e′ ratio. Finally, the last objective was to compare the reproducibility of LA emptying fraction and strain using both manual and post-processing methodology.

Methods

Study population

Stanford cardiomyopathy registry was established in 2003 and includes more than 5000 subjects with dilated, hypertrophic, and restrictive cardiomyopathy prospectively followed at Stanford University Medical Center. From this cohort, we randomly selected 225 subjects with HCM, DCM, and AMY of whom 50 of each group were further matched for mid-wall LS as well as age and sex between the groups of HCM and DCM. This matching would allow for better comparison of atrial function among groups. For comparison purposes, we also prospectively recruited 50 healthy volunteers from the community that were age and sex matched to the groups of HCM and DCM. The diagnosis of asymmetrical HCM was based on echocardiographic findings of a septal thickness of $>$13 mm and septal-to-posterior wall thickness ratio of $>$1.3, in the absence of any other cause that could account for the degree of hypertrophy.[10] The diagnosis of DCM was based on LVEF $<$45% in the absence of coronary disease. The diagnosis of AL amyloidosis was made by the biopsy of fat pad, gastrointestinal tract, kidney, or other involved tissue. The cardiac involvement was evaluated by expert opinion based on the combination of electrocardiogram findings (low; QRS amplitude $<$5 mm in limb leads or $<$10 mm in precordial leads, or relatively low voltage contrasting with echocardiographic LV hypertrophy aspect) in the setting of unexplained LV hypertrophy in a patient with histological evidence of AMY.[11] Patients with a diagnosis of atrial fibrillation on the day of echocardiogram testing were excluded, as this can confound the measurement of atrial remodelling or strain independent on ventricular adaptation.

Echocardiography

Echocardiography was performed using commercially available echocardiographic systems (Sonos 7500, iE33, and EPIQ 7C; Philips Medical Imaging, Eindhoven, The Netherlands). Standard echocardiographic views were obtained in M-mode and two-dimensional and colour tissue Doppler modes according to the guidelines of the American Society Echocardiography (ASE) recommendations.[12] Transmitral pulse Doppler velocities and tissue Doppler velocities of the mitral annulus were measured. LV end-systolic and end-diastolic volumes and LVEF were calculated with the use of the single-plane Simpson's method. Apical four-chamber view images were used to assess LV and LA functional parameters using both manual tracing and the software analysis.

When LVLS was measured using manual tracing, the endocardial borders in end-diastole and end-systole were traced manually from the septal to the lateral mitral annulus points.[13] Initial length (L_0) was obtained in end-diastole (peak of QRS) and final length (L_1) in end-systole. Manual LS was calculated as the formula: manual LS (%) $= 100 \times (L_1 - L_0)/L_0$. When LVLS was measured using the software, Image Arena™ (TOMTEC Imaging System, Unterschleissheim, Germany), the endocardial border was traced manually in end-diastole (at the peak of QRS) and the software automatically tracked the ventricular wall on subsequent frames in a selected beat.[14] Adequate tracking was verified and corrected by adjusting the region of interest on the contour. If significant deviation of contour from endocardium was still observed, the subject was excluded from the software analysis.

LA function consists mainly three functions: passive filling/reservoir function, passive emptying/conduit function, and active emptying/active function. As shown in *Figure 1*, to assess LA function, LA emptying fraction and the corresponding LA strain were used in this study. LA emptying fraction was calculated as follows[15]: total (%) $= 100 \times$ (LAVmax $-$ LAVmin)/LAVmax; active (%) $= 100 \times$ (LAVpreA $-$ LAVmin)/LAVpreA; and passive (%) $= 100 \times$ (LAVmax $-$ LAVpreA)/LAVmax, where LAV represents LA volume. Corresponding LA strain is calculated as follows: total (%) $= 100 \times$ (LALmin $-$ LALmax)/LALmax; active (%) $= 100 \times$ (LALmin $-$ LALpreA)/LALpreA; and passive (%) $= 100 \times$ (LALpreA $-$ LALmax)/LALmaxLA, where LAL represents LA length and all strain values are negative. When LA metrics were assessed by manual tracing, LAV was determined using the disk summation algorithm. LA inner border was traced excluding the area under the mitral valve annulus, the inlet of pulmonary veins, and the appendage. The length of LA wall was obtained by the same tracing.

When LA metrics were analysed by the software, pre-A was used as the reference point in this study. The LA contour was traced manually (*Figure 2A*), and the software automatically tracked the atrial wall on subsequent frames. Volume and strain curve were obtained as illustrated in *Figure 2B* and *C*. LA emptying fraction was calculated as follows using the length at pre-A as denominator to match the reference point (pre-A) to strain analysis: total (%) $= 100 \times$ (LAVmax $-$ LAVmin)/LAVpreA; active (%) $= 100 \times$ (LAVpreA $-$ LAVmin)/LAVpreA; and passive (%) $= 100 \times$ (LAVmax $-$ LAVpreA)/LAVpreA. In strain curve, a first negative peak strain represents LA contractile function (active). A second positive peak strain represents LA conduit function (passive). The sum of these values, LA strain sum, represents LA reservoir function (total) (*Figure 2C*).[4]

Intra- and interobserver variability and test–retest testing

For intraobserver variability, 60 subjects, including healthy subjects and patients with cardiomyopathy, were randomly selected and their data were re-analysed by the same investigator 2–4 weeks after the first analysis blinded to the initial tracings in both manual tracing and the software analysis. For interobserver variability, the same subjects were re-analysed by an independent second investigator. Intraclass correlation coefficient (ICC) and coefficient of variation (COV) were calculated for LVEF, LVLS, total LA emptying fraction, and total LA strain for manual tracing, and for LVEF, LVLS, total LA emptying fraction, and LA strain sum by the software analysis. We chose total LA metrics because the phase corresponds to LV metrics.

In addition, for further assessment of variability in both manual tracing and the software analysis, test–retest study was performed in 24 subjects including healthy subjects and patients with cardiomyopathy. Two sonographers acquired images of apical four-chamber view in each subject. ICC and COV were calculated for evaluating variability of LV and LA function parameters in both methods.

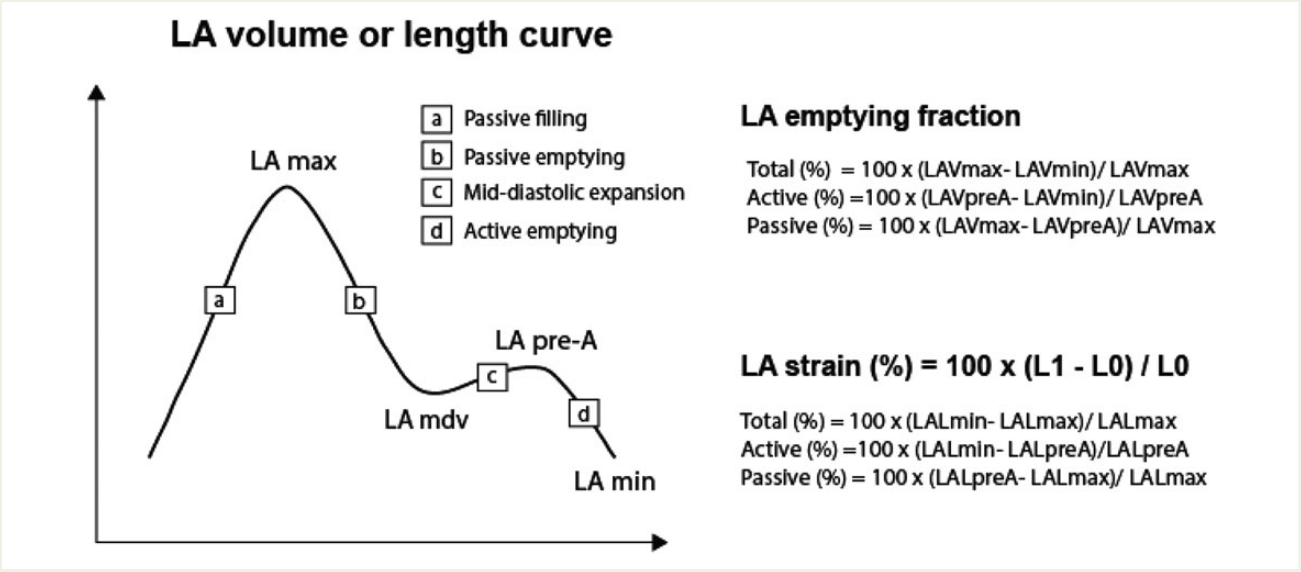

Figure 1 Concept of LA metrics. LA function is assessed in mainly three phases: passive filling/reservoir function, passive emptying/conduit function, and active emptying/active function. The LA emptying fraction and corresponding LA strain were obtained as the change ratio from the point of LAmax to LAmin for total, from LApreA to LAmin for active, and from LAmax to LApreA for passive. LAV, left atrial volume; LAL, LA length. Modified from Kiril A *et al.*[32]

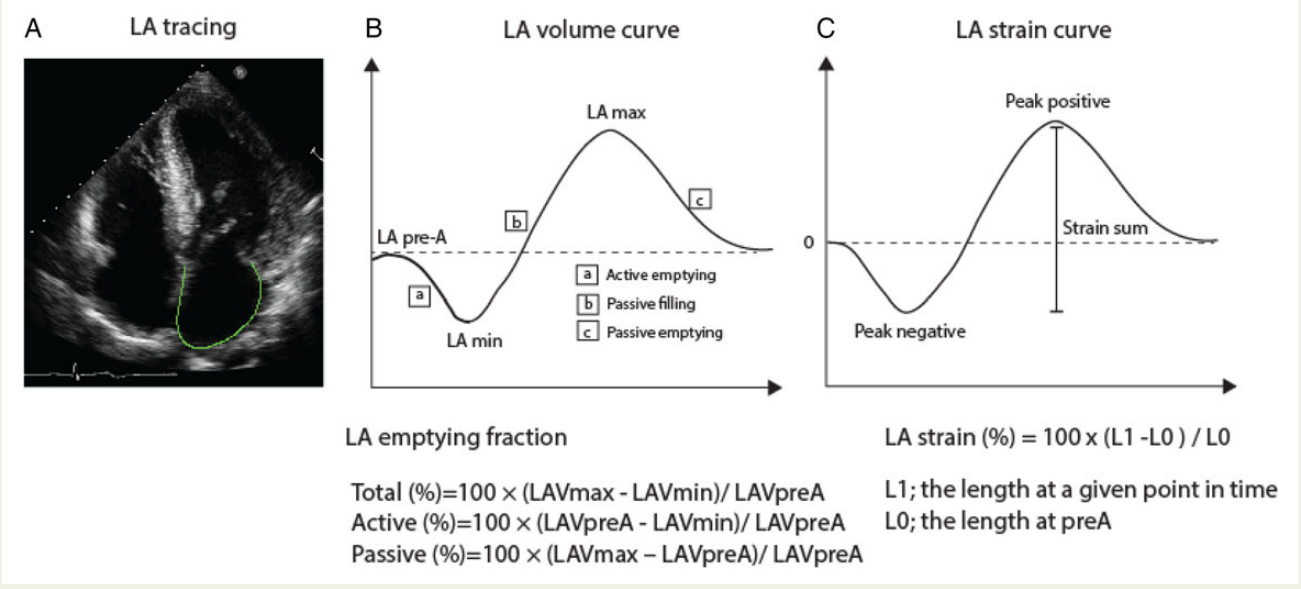

Figure 2 LA function assessment using the software. After tracking the LA wall (*A*), volume and strain curve were obtained (illustrated in *B* and *C*). Since pre-A is used as a reference point in assessing LA strain, LA emptying fraction was calculated using LAVpreA as denominator: total (%) = 100 × (LAVmax − LAVmin)/LAVpre-A; active (%) = 100 × (LAVpre-A − LAVmin)/LAVpre-A; and passive (%) = 100 × (LAVmax − LAVpre-A)/LAVpre-A. LAV, left atrial volume.

Statistical analysis

Variables are presented as counts and percentages or mean and standard deviation. Normality of the continuous variables was confirmed with Shapiro–Wilk test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. One-way ANOVA test was used among subgroups, and *post hoc* analysis was performed with Turkey-HSD multiple comparison tests or Games–Howell, as appropriate. Correlations between EF and strain of LV and LA were calculated using Pearson's correlation coefficient, and Fisher r-to-z transformation was used to evaluate the significance between

two correlation coefficients. Correlation was defined as strong if $|r| \geq 0.7$, moderate if $0.5 \leq |r| < 0.7$, and weak if $0.3 \leq |r| < 0.5$. We performed stepwise multiple regression analysis to assess the independent correlations of LA strain with age, sex, BSA, BMI, lateral E/e′ ratio, endocardial LVLS, mean blood pressure, and heart rate. Then, LA strain sum was compared among the cardiomyopathy groups after examining the residuals. A two-sided *P*-value of <0.05 was considered significant. All analyses were performed using SPSS 21 software® (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the clinical and echocardiographic characteristics of our study population. The proportion of male was comparable among all groups. The age of patients in AMY group was significantly higher than in the other groups. We were able to derive LVLS and LA strain using the manual tracing in all subjects. On the other hand, using the software we succeed in analysis of LVLS in 197 (98.5%) subjects (50 in DCM, 48 in HCM, 50 in AMY, and 49 in controls) and of LA strain in 187 (93.5%) subjects (47 in DCM, 47 in HCM, 46 in AMY, and 47 in controls). Mid-wall LVLS was comparable among the cardiomyopathy groups by design of the study, while endocardial LVLS was the lowest in the DCM group. LA emptying fraction and LA strain were impaired in patients with any cardiomyopathy compared with controls, derived from both manual tracing and the software analysis (*Table 2*).

Relationship between LV and LA strain and volumetric fraction metrics

Overall, a moderate correlation was found between LVEF and endocardial LVLS ($r = -0.51$, $P < 0.001$, *Figure 3*), and the correlation was stronger in patients with LVEF <50% ($r = -0.52$, $P < 0.001$) than with LVEF ≥50% ($r = -0.20$, $P = 0.02$); the comparison between these two relationship was statistically different (Fisher r-to-z transformation, $P = 0.02$). In contrast, a strong relationship was found between LA emptying fraction and corresponding strain measured using both manual tracing (total LA emptying fraction and LA strain: $r = -0.83$; active LA emptying fraction and LA strain: $r = -0.89$; and passive LA emptying fraction and LA strain: $r = -0.71$; all $P < 0.001$, *Figure 4A–C*) and the software analysis (total LA emptying fraction and LA strain sum: $r = 0.87$; active LA emptying fraction and negative LA strain: $r = -0.87$; and passive LA emptying fraction and positive LA strain: $r = -0.83$; all $P < 0.001$, *Figure 4D–F*). This strong correlation was observed regardless of the aetiology or analysis method; the correlations between LA emptying fraction and strain were −0.92, −0.88, and −0.95 on using manual tracing, and −0.84, −0.77 and, −0.84 on using the software analysis, for DCM, HCM, and AMY, respectively.

Relationship between LA strain and LV function and correlates of LA strain

We found a moderate relationship between LA strain sum and LVLS ($r = -0.65$, $P < 0.001$, *Figure 5A*) followed by septal E/e′

Table 1 Characteristics of enrolled patients

	Controls (*n* = 50)	DCM (*n* = 50)	HCM (*n* = 50)	AMY (*n* = 50)
Age (years)	51.0 ± 11.8	51.6 ± 12.0	50.6 ± 13.1	66.5 ± 8.1******
Male, *n* (%)	29 (58)	29 (58)	27 (54)	34 (68)
BSA (m^2)	1.9 ± 0.2	2.0 ± 0.3	2.0 ± 0.3*	1.9 ± 0.2***
BMI (kg/m^2)	26.1 ± 3.3	30.3 ± 6.7*	32.3 ± 8.5*	26.3 ± 4.7******
Heart rate (bpm)	64.1 ± 9.4	72.8 ± 13.5*	73.0 ± 18.2*	79.0 ± 13.5*
Systolic blood pressure (mmHg)	123.5 ± 12.9	106.3 ± 22.3*	124.6 ± 19.8**	119.6 ± 19.1**
Diastolic blood pressure (mmHg)	75.5 ± 8.8	72.1 ± 13.7	72.7 ± 10.9	68.2 ± 12.1*
Mean blood pressure (mmHg)	91.5 ± 9.3	83.1 ± 12.6*	92.0 ± 12.0**	85.6 ± 13.6*
Echo parameters				
Interventricular septum (cm)	0.7 ± 0.1	0.9 ± 0.2*	2.0 ± 0.5***	1.5 ± 0.3******
Posterior wall (cm)	0.7 ± 0.1	1.0 ± 0.2*	1.3 ± 0.3***	1.6 ± 0.9***
LV dimension (cm)	4.8 ± 0.4	6.2 ± 1.0*	4.2 ± 0.6***	3.9 ± 0.9***
Relative wall thickness	0.3 ± 0.1	0.3 ± 0.1	0.8 ± 0.2***	1.0 ± 0.9***
LV function				
LV ejection fraction (%)	62.4 ± 4.8	33.1 ± 8.2*	68.8 ± 6.2***	59.9 ± 9.6*****
Mid-wall LVLS (%)	−19.6 ± 1.5	−12.3 ± 2.0*	−13.4 ± 1.7*	−12.7 ± 3.4*
Endocardial LVLS (%)	−20.5 ± 2.2	−12.0 ± 2.0*	−15.1 ± 4.3***	−14.5 ± 4.4***
Septal E/e′	8.0 ± 2.0	15.1 ± 7.2*	21.6 ± 9.5***	18.5 ± 6.7*
Lateral E/e′	6.1 ± 1.6	11.8 ± 5.6*	15.4 ± 8.5***	16.1 ± 8.0***
LA size				
Maximal LA volume index (mL/m^2)	25.6 ± 6.7	39.8 ± 21.3*	49.6 ± 19.1*	33.5 ± 12.4***

DCM, dilated cardiomyopathy, HCM, hypertrophic cardiomyopathy, AMY, amyloidosis, BSA, body surface area, LV, left ventricular, LS, longitudinal strain, LA, left atrial.
*$P < 0.05$ vs. controls.
**$P < 0.05$ vs. DCM.
***$P < 0.05$ vs. HCM.

Table 2 LA emptying fraction and LA strain using both methods

	Controls	DCM	HCM	AMY
Manual tracing				
Number	50	50	50	50
Total LA emptying fraction (%)	62.7 ± 6.2	46.4 ± 14.2*	43.4 ± 11.8*	44.5 ± 16.2*
Active LA emptying fraction (%)	38.2 ± 5.3	27.8 ± 12.6*	26.2 ± 10.2*	27.5 ± 14.6*
Passive LA emptying fraction (%)	39.5 ± 9.2	26.4 ± 10.77*	23.7 ± 8.1*	24.4 ± 11.0*
Total LA strain (%)	−28.2 ± 8.6	−18.3 ± 6.9*	−17.4 ± 5.2*	−17.5 ± 7.5*
Active LA strain (%)[a]	−13.6 ± 2.3	−9.4 ± 4.7*	−9.1 ± 3.9*	−9.2 ± 5.4*
Passive LA strain (%)	−17.3 ± 9.4	−9.9 ± 4.9*	−9.1 ± 3.6*	−9.2 ± 4.4*
Software analysis				
Number	49	47	47	46
Negative LA strain (%)[a]	−14.1 ± 3.8	−9.3 ± 4.7*	−9.2 ± 4.4*	−9.3 ± 4.7*
Positive LA strain (%)	26.8 ± 9.5	12.2 ± 7.3*	14.3 ± 7.3*	11.6 ± 6.1*
LA strain sum (%)	41.0 ± 9.7	21.3 ± 10.6*	24.0 ± 7.7*	21.1 ± 9.8*

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; AMY, amyloidosis; LA, left atrial.
[a]Active LA strain and negative LA strain are comparable due to using the same reference (pre-P).
*$P < 0.05$ vs. controls.

($r = -0.59$, $P < 0.001$) or lateral E/e′ ($r = -0.50$, $P < 0.001$). In multivariate multiple regression analysis including age, sex, BSA, BMI, lateral E/e′ ratio, endocardial LVLS, mean blood pressure, and heart rate, we found that LVLS ($B = -1.38$, $\beta = -0.48$, $P < 0.001$), lateral E/e′ ($B = -0.43$, $\beta = -0.24$, $P < 0.001$), age ($B = -0.21$, $\beta = -0.21$, $P < 0.001$), and heart rate ($B = -0.13$, $\beta = -0.14$, $P = 0.02$) were independent correlates of LA strain sum ($R^2 = 0.53$, $P < 0.001$). Using this model, we compared LA strain sum among aetiologies taking into account the correlates previously found. After adjustment for the correlates, LA strain sum was still comparable among aetiologies (25.6 ± 7.6% in DCM, 25.2 ± 10.0% in HCM, and 26.4 ± 8.3% in AMY, ANOVA $P = 0.82$). Even when comparison was performed including controls, LA strain sum did not differ significantly (29.8 ± 7.8% in controls, 26.0 ± 7.6% in DCM, 25.3 ± 10.1% in HCM, and 26.6 ± 8.4% in ANOVA, ANOVA $P = 0.06$) (*Figure 5B* and *C*). Similar results were found after excluding AMY group, the age of which was higher than the others (adjusted LA strain sum: 30.9 ± 7.8% in controls, 28.0 ± 7.5% in patients with DCM, and 27.5 ± 10.5% in HCM, ANOVA $P = 0.13$).

Intra- and interobserver variability and test–retest study

Since LA active strains obtained by both manual tracing and the software are calculated using the same reference (pre-A), we chose this parameter for comparison between these methodologies. Strong correlation was found between the values of active LA strain derived from both methods with the bias (95% CI) of 0.03% (−6.7%, 6.8%) ($r = 0.75$, $P < 0.001$).

Table 3 summarizes the intra- and interobserver variability in total LVEF, endocardial LVLS, total LA emptying fraction, and LA strain derived from both manual tracing and the software analysis. In LV parameters, all COVs in the table were <6 with ICCs of high reliability. For LA parameters, all COVs in the table were <13% with ICCs of high reliability. COVs in LV parameters were smaller than COVs in LA parameters. *Table 4* shows the strain variability of test–retest study in left ventricle and atrium. For LVLS, both endocardial and mid-wall LVLS had a smaller variability between images acquired by different investigators. Compared with LVLS, LA strain had a larger variability in both manual tracing and the software analysis. The Bland–Altman plots of assessing LA function are shown in *Figure 6*.

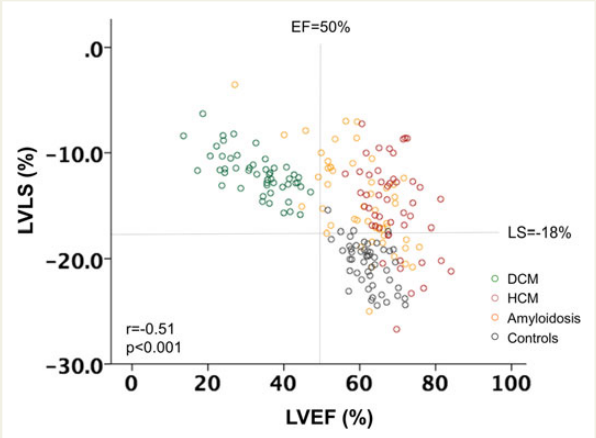

Figure 3 Correlation between LVEF and endocardial longitudinal strain (LVLS). Overall, moderate correlation was found between LVEF and LVLS ($r = -0.51$, $P < 0.01$). Patients with HCM or amyloidosis with preserved LVEF presented decreased or normal LVLS in absolute value despite a preserved LVEF. On the other hand, patients with DCM presented decreased LVLS in absolute value. No subjects presented reduced LVEF and preserved LVLS.

Discussion

The main finding of our study is that in contrast to the moderate relationship between LVEF and LVLS, there is a strong linear

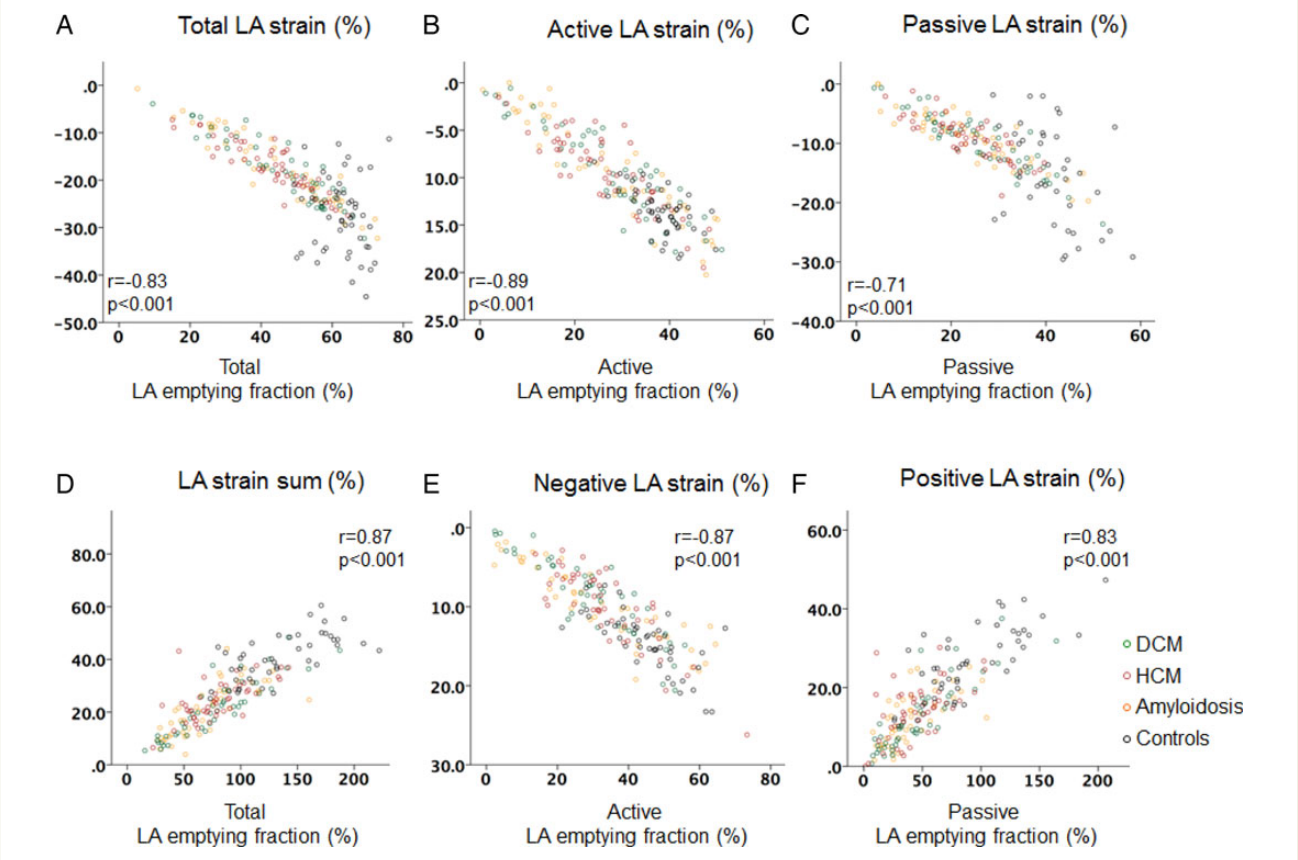

Figure 4 Overall correlation between LA emptying fraction and LA strain in three-atrial phases by manual tracing and the software. Upper panels (*A*–*C*) show the correlation assessed using manual tracing. Strong correlation was found between (*A*) total LA emptying fraction and total LA strain ($r = -0.83$, $P < 0.001$), (*B*) active LA emptying fraction and active LA strain ($r = -0.89$, $P < 0.001$), and (*C*) passive LA emptying fraction and passive LA strain ($r = -0.71$, $P < 0.001$). Lower panels (*D*–*F*) show the correlation assessed using the software. Strong correlation was found between (*D*) total LA fraction and LA strain sum ($r = 0.87$, $P < 0.001$), (*E*) active LA emptying fraction and negative LA strain ($r = -0.87$, $P < 0.001$), and (*F*) passive LA emptying fraction and positive LA strain ($r = 0.83$, $P < 0.001$). In panels (*D*–*F*), negative LA strain corresponds to active LA strain using manual tracing. Positive LA strain corresponds to passive LA strain using manual tracing. LA strain sum, the sum of these values, corresponds to total LA strain using manual tracing.

correlation between LA emptying fraction and LA strain. This strong relationship has both physiological and clinical implications and likely reflects chamber-specific myofibre architecture.[8,9] Our study also compares the reproducibility of LA and LV functional metrics.

In recent years, more attention has been given to the left atrium in cardiovascular medicine. While initially viewed as a passive chamber, atrial dynamics is emerging as an important prognostic factor for incident atrial fibrillation as well as cardiovascular events (*Table 5*). In view of the incremental value of strain imaging of the left ventricle, several investigators have applied deformation imaging to the left atrium with the objective to better define atrial dynamics in healthy subjects first[7,23] and then in pathological conditions. For example, D'Andrea *et al.* demonstrated that speckle tracking could be applied to assess LA function in patients with DCM.[16] In patients with heart failure with preserved EF, Santos *et al.*[19] demonstrated that LA emptying fraction and LA strain was significantly decreased, even after adjustment for potential confounders, despite normal LA volume; Freed *et al.*[21] demonstrated that abnormal LA mechanical indices, particularly LA reservoir strain, are independently associated with cardiac event. In patients with coronary artery disease and preserved LVEF, Welles *et al.*[17] demonstrated that LA dysfunction assessed by LA function index (LAFI), which incorporates measures of LA emptying fraction, could predict heart failure hospitalization. They further suggested that the LAFI might be useful for heart failure risk stratification. LA function has also been used as a surrogate marker of filling pressure as a result of haemodynamic overload and mechanical stretch of the LA wall. Hirose *et al.*[18] demonstrated that active LA emptying function was an independent predictor of new-onset atrial fibrillation in patients with risk factors in a prospective study. In studies by Wakami *et al.*[24] and Cameli *et al.*,[25] LA longitudinal deformation was correlated with LV filling pressure better than E/e′ ratio, which is typically used to evaluate LV filling pressure in both patients with heart failure and preserved or reduced LVEF. Thus, LA functional metrics appear to be in line to previously demonstrated metrics such as E/e′ ratio. Moreover, this has also prompted the interest in looking at parameters that incorporate LA function and E/e′ ratio often referred to as LA stiffness measures.[26,27] As shown in these studies, some authors use LA emptying

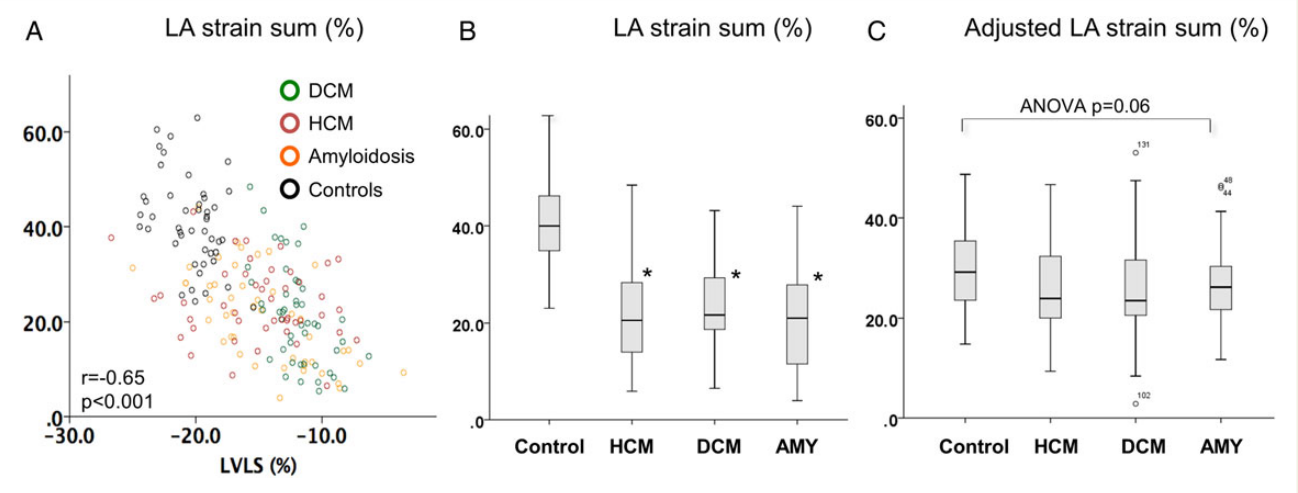

Figure 5 Correlation with LVLS and the difference among groups in LA strain sum. (*A*) Moderate correlation between LVLS and LA stain sum ($r = -0.65$, $P < 0.001$). (*B*) LA strain sum of patients with cardiomyopathy was impaired compared with controls. (*C*) However, once adjusted by the correlates, there was no significant difference among all groups including controls. *$P < 0.001$ vs. controls. LV, left ventricular; LS, longitudinal strain; LA, left atrial.

Table 3 Intra- and interobserver variability in LV and LA parameters

	Mean ± SD	Bias	LOA	ICC (95% CI)	COV
Intraobserver variability ($n = 60$)					
Left ventricle					
Manual-LVEF (%)	51.7 ± 18.6	−0.2	−7.5 to 7.1	0.99 (0.98–0.99)	3.4
Manual-4ch-LS (%)	−16.8 ± 5.5	0.3	−2.8 to 3.4	0.98 (0.96–0.99)	3.5
Software-LVEF (%)	51.3 ± 17.6	0.9	−5.2 to 7.0	0.99 (0.99–1.00)	2.6
Software-4ch-LS (%)	−16.2 ± 5.5	−0.2	−3.5 to 3.1	0.98 (0.96–0.99)	3.2
Left atrium					
Manual-total LA emptying fraction (%)	48.0 ± 14.4	1.7	−9.7 to 13.1	0.96 (0.93–0.97)	5.1
Manual-total LA strain (%)	−19.9 ± 7.9	−0.8	−8.8 to 7.2	0.93 (0.89–0.96)	7.6
Software-total LA emptying fraction (%)	97.5 ± 51.7	0.8	−38.0 to 39.6	0.96 (0.93–0.98)	7.4
Software-LA strain sum (%)	27.8 ± 12.7	0.2	−9.4 to 9.8	0.97 (0.94–0.98)	6.5
Interobserver variability ($n = 60$)					
Left ventricle					
Manual-LVEF (%)	51.5 ± 17.8	0.2	−13.5 to 13.9	0.96 (0.94–0.98)	5.7
Manual-4ch-LS (%)	−16.3 ± 5.2	−0.6	−5.1 to 3.9	0.95 (0.91–0.97)	4.6
Software-LVEF (%)	50.6 ± 18.1	1.1	−7.1 to 9.3	0.99 (0.98–0.99)	3.6
Software-4ch-LS (%)	−16.0 ± 5.3	−0.6	−3.7 to 2.5	0.98 (0.95–0.99)	3.6
Left atrium					
Manual-total LA emptying fraction (%)	51.1 ± 13.5	−1.3	−17.0 to 14.4	0.91 (0.85–0.95)	7.4
Manual-total LA strain (%)	−21.6 ± 7.7	0.8	−10.0 to 11.6	0.87 (0.78–0.92)	12.6
Software-total LA emptying fraction (%)	85.5 ± 45.3	10.7	−26.7 to 48.1	0.93 (0.87–0.96)	9.5
Software-LA strain sum (%)	27.8 ± 13.0	0.2	−13.1 to 13.5	0.95 (0.87–0.94)	9.8

ICC, intraclass correlation coefficient; LOA, limits of agreement; COV, coefficient of variation; LA, left atrial; LV, left ventricular; EF, ejection fraction; LA, longitudinal strain.

fraction and others LA strain either individually or incorporated in scores.

Our study focused on better understanding of the complementarity between volumetric and deformation parameters of the left atrium and its relationship to LV metrics in patients with heart failure. Our study has two main clinical and physiological implications. First, the strong collinearity between LA emptying fraction and LA strain will likely lead to comparable diagnostic or outcome

Table 4 Test–retest study in strain measurement for left ventricle and left atrium

	Mean ± SD	Bias	LOA	ICC (95% CI)	COV
Left ventricle ($n = 24$)					
Manual-endocardial LS (%)	−15.2 ± 4.4	−0.1	−4.2 to 4.0	0.94 (0.87–0.98)	5.8
Manual-mid-wall LS (%)	−13.3 ± 4.0	−0.1	−3.0 to 2.8	0.96 (0.91–0.98)	4.5
Software-endocardial LS (%)	−14.6 ± 5.3	−0.1	−3.6 to 3.4	0.97 (0.93–0.99)	4.5
Software-mid-wall LS (%)	−12.8 ± 5.1	−0.2	−3.9 to 3.5	0.96 (0.91–0.98)	4.7
Left atrium ($n = 24$)					
Manual-total LA emptying fraction (%)	47.9 ± 11.2	1.3	−21.0 to 23.6	0.80 (0.54–0.91)	12.4
Manual-total LA strain (%)	−19.1 ± 6.6	0.1	−8.3 to 8.5	0.90 (0.76–0.96)	10.3
Software-total LA emptying fraction (%)	88.5 ± 41.3	2.2	−65.0 to 69.4	0.79 (0.51–0.91)	15.3
Software-total LA strain (%)	25.5 ± 13.0	−0.2	−15.3 to 14.9	0.88 (0.72–0.95)	10.1

ICC, intraclass correlation coefficient; LOA, limits of agreement; COV, coefficient of variation; LS, longitudinal strain; LA, left atrial.

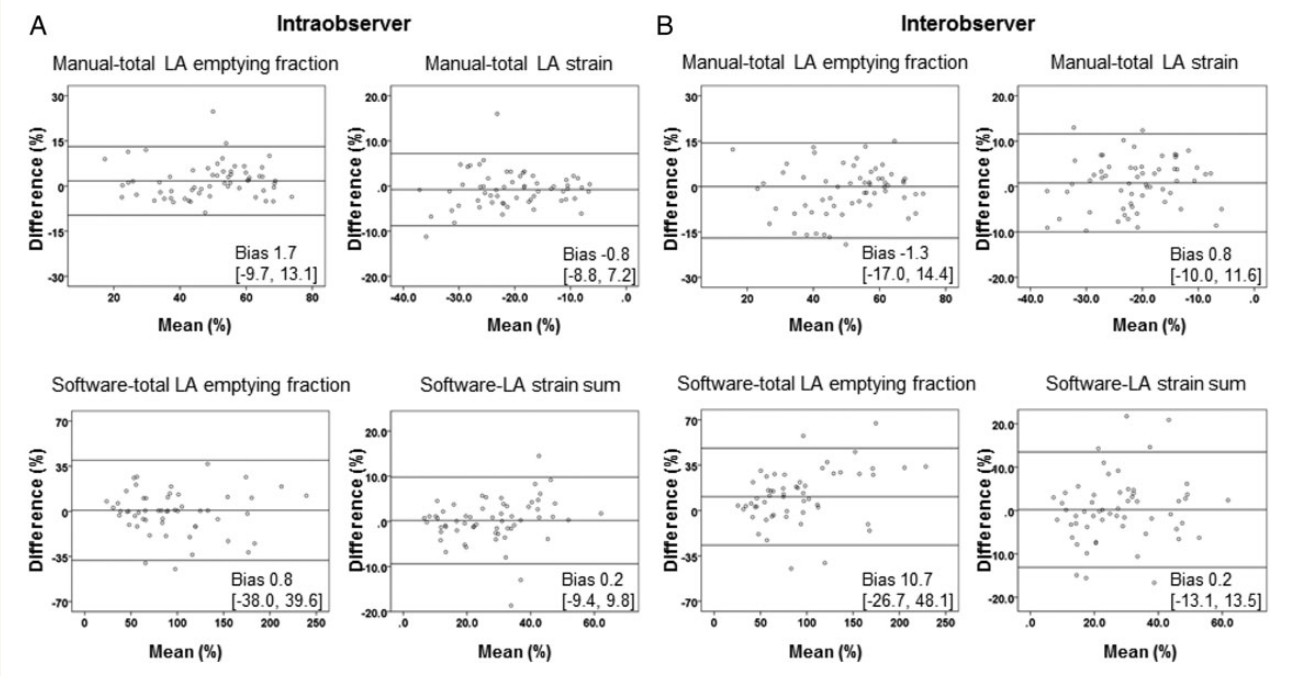

Figure 6 Bland–Altman plot for intra- and interobserver assessment in LA parameters.

predictive value of them; this will need to be further validated in future studies. The main difference between the two metrics would however lie in the reproducibility of technique in individual laboratories. In contrast to this relationship, LVEF and LVLS are not as strongly related to each other; this is especially true in conditions where the left ventricle is not dilated and usually when LVEF >50%. From a pathophysiological point of view, the left atrium often dilated with disease progression and we rarely observe clinically a hypertrophied left atrium without any evidence of enlargement. The myofibre architecture could also explain chamber-specific differences between volumetric and longitudinal deformation. The left ventricle consists of three layers of myocardial fibre, and different susceptibility of longitudinal and circumferential myocardial fibres to ischemia, hypertrophy, infiltrations, or increase in afterload has been reported with the longitudinal fibres being the most vulnerable.[28,29] In contrast to the left ventricle, the left atrium consists of two thin layers of myofibre: intermingling circumferential and longitudinal muscular bundles; this could explain why alteration in longitudinal shortening may be closely related to transverse shortening and volumetric changes but this has to be more comprehensively studied.[8,9]

Second, the study highlights that atrial function is not *per se* independent on LV function. In fact, both chambers are anatomically related together by the atrio-ventricular groove or annulus junction

Table 5 Previous studies using LA function parameters

Author	Population	Number	Parameter	Finding
D'Andrea *et al.* 2009[16]	DCM	314	LA strain	LA strain is associated with peak VO_2 (β coefficient with peak $VO_2 = 0.59$)
Welles *et al.* 2012[17]	CAD	855	LA function index (LAFI)[a]	LAFI is independently associated with heart failure hospitalization (adjusted HR of every SD decrease in LAFI: 2.0)
Hirose *et al.* 2012[18]	Patients with risk factors[b]	580	LA emptying fraction	Active LA emptying function was a predictor of new-onset atrial fibrillation (OR: 0.73, $P < 0.001$)
Santos *et al.* 2014[19]	HFpEF	135	LA strain	LA strain was decreased independent of LA size in patients with HFpEF ($P = 0.002$). Patients with worse LA strain had more heart failure hospitalization
Biering-Sorensen *et al.* 2014[20]	Patients with cryptogenic stroke	58	LA emptying fraction	The risk of subsequently being diagnosed with paroxysmal atrial fibrillation is increased with decreasing tertile of the LA emptying fraction (HR: 9.6)
Freed *et al.* 2016[21]	HFpEF	308	LA strain	Cardiac outcome is increased with decreasing the LA emptying fraction (adjusted HR of every SD decrease in LA strain: 1.6)
Hsu *et al.* 2016[22]	Persistent AF	190	LA strain	Adding E/LA strain and LA strain to already known predictors improved the values in predicting cardiovascular events

DCM, dilated cardiomyopathy; LA, left atrial; HF, heart failure; CAD, coronary artery disease; HFpEF, heart failure preserved ejection fraction; OR, odds ratio; HR, hazard ratio.
[a]LAFI = (LA emptying fraction × LVOT VTI)/(LAESV indexed to BSA) (cm × (m^2)/mL), where LVOT VTI is velocity time integral of the left ventricular outflow tract (cm), LAESV is maximal left atrial volume in end-systole (mL), and BSA is body surface area.
[b]Patients were prospectively enrolled who needed medications for one or more risk factors such as hypertension, type 2 diabetes mellitus, dyslipidaemia, coronary artery disease, mild mitral regurgitation or other valvular heart disease, heart failure or arrhythmias or other than atrial arrhythmias, and patients with ECG abnormalities.

and functionally by the effective filling and stroke volume of the cardiovascular system. In the presence of limited annular expansion due to the ventricular dysfunction will also limit the dynamic atrial motion. In addition, as was shown in the model, other factors such as E/e′ ratio as surrogate for ventricular pressure will also influence atrial function. For studies comparing atrial function between aetiologies, careful propensity matching to account for differences in LV strain or E/e′ should be performed to determine whether intrinsic atrial function is different as was highlighted by our study.

Our study also brings important methodological consideration, demonstrating the good reproducibility of LA emptying fraction or LA strain albeit not as strong as LVEF and LV strain. Both methods of assessing LA emptying fraction and LA strain demonstrated acceptable reproducibility with a small trend of better reproducibility of measurements obtained by the software. The possible reason may be due to the differences between the observers or within the observer in extent of excluding the appendage and pulmonary vein from LA cavity for manual tracing. On the other hand, we have to trace a similar contour for the software analysis to optimize the tracking. In terms of the test–retest study, larger variability of LA strain than LVLS was found. This may be explained by the clinical settings in which the echocardiography typically focuses more on the left ventricle than the left atrium when acquiring apical four-chamber view. However, if LA images were adequately prioritized, test–retest variability would likely be better.

There are some limitations in our study. First, only apical four-chamber view was assessed in this study. However, the study was mainly intended as a proof of concept study focusing on the commonly obtained measures in clinical practice and should be sufficient for the purpose of the study. Further studies of global longitudinal strain from apical four-, three-, and two-chamber views or global LA strain from apical four- and two-chamber views or especially three-dimensional strain are needed to confirm these results.[4,30,31] Second, LA strain assessment by the software is an off-label indication. Although reference values reported so far for LA strain were obtained in relatively small groups, the values in healthy controls obtained in our study are comparable to these values.[4]

In summary, our findings show LA longitudinal strain correlates with LA emptying fraction regardless of the aetiology of cardiomyopathy in contrast to the correlation between LVEF and LVLS. This may be due to the structural and morphological difference in LV and LA structures as well as remodelling of the LA in heart failure.

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