Left atrium strain parameters in light chain cardiac amyloidosis and hypertensive heart disease

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March 16, 2023

Abstract

Background: Longitudinal strain is helpful in discriminating between cardiac amyloidosis and other causes of left ventricle hypertrophy. We aimed to compare left atrial strain between light chain cardiac amyloidosis (AL-CA) and hypertensive heart disease (HHD). **Methods:** Echocardiography was performed at 21 consecutive AL-CA patients, 56 HHD patients and 21 controls who were enrolled in the current study between April 2018 and January 2021. Echo PAC workstation was employed to analyze LA strain of all the participants. Standard echocardiographic parameters and LA strain parameters were compared between AL-CA and HHD patients. ROC curves were employed to assess the discriminating ability of LA strain. **Results:** LASr and LASct were significantly lower (21.03 vs 26.17, P =0.009, and 12.11 vs 15.51, P=0.009, respectively) in AL-CA group than those in HHD group, whereas LAScd and SD-TPS were similar between the two groups (P=0.17 and P=0.27, respectively). The cutoff points of LASr and LASct for discriminating between AL-CA and HHD were 19.53% and 11.34%, respectively. **Conclusions:** AL-CA patients had marked reductions in LASr and LASct. LA strain had additional value in differentiating AL-CA from HHD patients.

Introduction

Amyloidosis is a constellation of diseases characterized by misfolded proteins deposited in target organs[1]. Cardiac involvements were thought to be very rare previously but are now understood to be underdiagnosed[2]. Acquired monoclonal immunoglobulin light-chain (AL); hereditary, mutated transthyretin-related (ATTRm); and wild-type transthyretin-related (ATTRwt) are considered as three major types of cardiac amyloidosis[3]. Light chains cardiac amyloidosis (AL-CA) progresses much faster than other types of amyloidosis, and appropriate treatment is capable of prolonging survival time substantially[1,4].

Traditionally, AL-CA can be diagnosed by pathologic confirmation of immunoglobulin light chain amyloid in extracardiac tissue and cardiac imaging consistent with cardiac amyloidosis (CA)[5]. Echocardiography often provides first clues to the presence of CA, and is helpful for prompting a low threshold for further multimodality assessment[2,6].

Cardiac amyloid can virtually infiltrate all cardiac chambers[7,8]. Previous studies have shown the significant enlargement of LA and reduction of left atrial strain in CA patients[9-14]. Possible mechanisms include restrictive LV physiology with elevated filling pressure resulting from intramyocardial amyloid infiltration and intrinsic LA failure due to direct amyloid infiltration[10]. Similarly, increased LA volume is a marker of hypertensive heart disease (HHD), and significant reduction of LA strain occurs in HHD patients[15]. A study containing 11 AL-CA patients, 33 ATTR-CA patients, and 25 HHD patients showed that HHD group had significantly higher left atrial strain values than the amyloid cases[9]. However, the number of AL-CA patients in that study was small. Meanwhile, patients with atrial fibrillation (AF) had reduced left atrial strain values, which were not studied separately in that study[9]. The aim of this study was to evaluate the differences in left atrial strain between patients with AL-CA and those with HHD.

Methods

Study population

We prospectively collected 25 consecutive patients who hospitalized for multiple myeloma and diagnosed with AL-CA between April 2018 and January 2021 in the First Affiliated Hospital of Soochow University. The diagnosis of AL-CA was established on the basis of a characteristic echocardiogram for amyloid and a histological proof of presence of systemic amyloid, in the absence of any other plausible causes of LV hypertrophy[10]. 3 patients with AF and one with poor imaging were excluded. As a result, 21 patients with AL-CA were enrolled in our study. HHD group consisted with 56 randomly selected patients with hypertensive heart disease matched with age, gender and left ventricular mass index (LVMI). The diagnosis of hypertensive heart disease was based on echocardiographic demonstration of a hypertrophic LV and a history of systemic hypertension in the absence of other cardiac or systemic disease[16]. Additionally, 25 age- and gender- matched subjects with normal electrocardiography served as a control group.

Echocardiography

The two-dimensional echocardiographic imaging of all patients was performed by GE Vivid E95 equipment (Norway) 3.5 MHz transducer (M5S). Patients were placed in the lateral decubitus position. Electrocardiogram and echocardiography were recorded simultaneously. Measurements were performed according to the guidelines of the American Society of Echocardiography [17]. Left ventricular end-systolic diameter and left atrial anteroposterior dimension were measured at end-systole, and left ventricular end-diastolic diameter was measured at end-diastole on parasternal views. End-diastolic septal thickness and posterior wall thickness were assessed on both parasternal views and short axis views. Left ventricular ejection fraction (LVEF) and left atrial ejection fraction were obtained by the biplane Simpson's method on apical 4-chamber and 2-chamber views. Pulse-wave doppler (PW) was used to measure the peak early diastolic flow velocity (E peak), peak late diastolic flow velocity (A peak) and E/A ratio of mitral valve. PW was also used to measure the e' of septal and lateral wall and E/e' in tissue doppler imaging (TDI) mode. Tricuspid regurgitation velocity (TR velocity) was measured by continuous doppler (CW) under the guidance of color doppler on apical 4-chamber views.

LA longitudinal strain analysis

Analysis of two-dimensional speckle tracking echocardiograms was performed using Echo PAC workstation (GE, USA). The images of apical 4-chamber and 2-chamber, which could clearly show the left atrium, were used to analyze left atrial strain by Q-Analysis method. Region of interest (ROI) should include all left atrial myocardium but without pericardium, so the ROI width is usually [?]3mm. Once the region of ROI was established, the analyzer modified the region to ensure the quality of speckle tracking (See Figure1). SD-TPS was used to measure the degree of LA dispersion. It was calculated as the SD of time to peak and expressed as a percentage of the R-R interval[18].

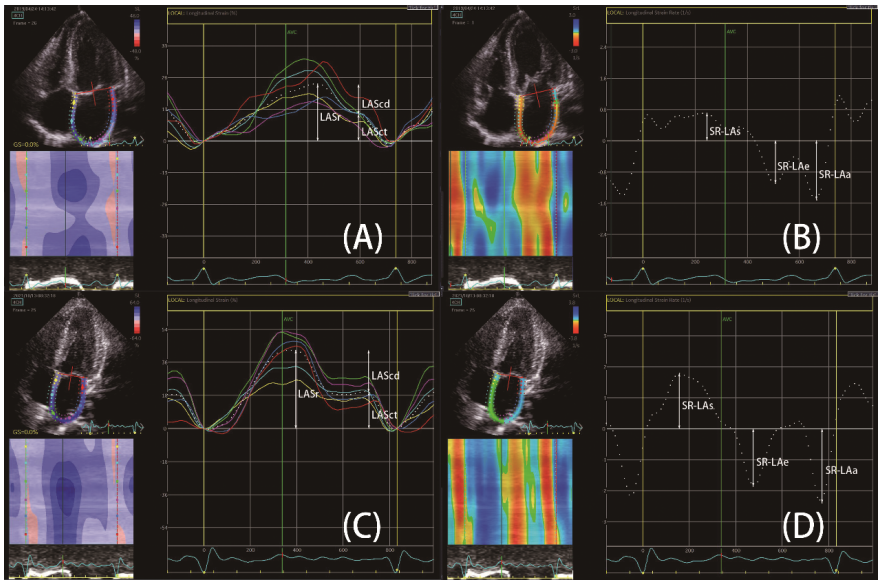

Figure 1. LA strain and strain rate curves from a patient with AL-CA and a patient with HHD. Figure 1(A): LA strain parameters from a patient with AL-CA. Figure 1(B): LA strain rate parameters from a patient with AL-CA. Figure 1(C): LA strain parameters from a patient with HHD. Figure 1(D): LA strain rate parameters from a patient with HHD.

Statistical analysis

Shapiro–Wilk test were used to test continuous variables for normality. Continuous variables conforming to normality were expressed as mean (standard deviation, SD) and compared using student's t test. Continuous variables failing to conform to normality were expressed as median (interquartile range, IQR) and compared using Wilcoxon rank-sum test. Categorical variables were expressed as frequencies (percentages) and compared using Pearson's chi-squared test. Receiver operating characteristic (ROC) curves were employed to assess the ability of LASr and LASct for discriminating between AL-CA and HT patients. Pearson's correlation coefficient was used to evaluate the correlation between LA function and LV structure, LV function, and LA size. All analyses were performed using Stata version 15.1. All p-values and confidence intervals were two-sided.

Results

Demographics and clinical characteristics

A total of 102 patients were enrolled in the current study. Table 1 showed that demographic characteristics were overall balanced between AL-CA group and HHD group. Compared with AL-CA group, HHD patients were more likely to have higher SBP (147.96 vs 115.43, P <0.001), DBP (88.00 vs 72.00, P <0.001), and MAP (107.33 vs 86.67, P <0.001).

Table 1. Demographics and clinical characteristics

Factor	AL-CA	HHD	p-value	Control
	N=21	N=56	AL-CA vs HT	N=25
Gender			0.69	
Female	4 (19.05%)	13 (23.21%)		9 (36.00%)
Male	17 (80.95%)	43 (76.79%)		16 (64.00%)
Age, years	59.00 (9.22)	58.93 (14.04)	0.98	54.92 (14.87)

Factor	AL-CA	HHD	p-value	Control
SBP, mmHg	115.43 (14.04)	147.96 (19.07)	<0.001	124.58 (12.04)
DBP, mmHg	72.00 (6.00)	88.00 (19.00)	<0.001	80.00 (12.50)
MAP, mmHg	86.67 (4.34)	107.33 (17.33)	<0.001	94.67 (11.33)
Height, cm	170.00 (12.00)	168.00 (6.50)	0.66	168.00 (10.00)
Weight, kg	65.01 (7.11)	68.96 (7.33)	0.037	63.64 (11.23)
BSA, m^2	1.85 (0.18)	1.90 (0.15)	0.069	1.78 (0.22)

Note: SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean artery pressure, BSA body surface area.

Standard echocardiographic parameters

Table 2 compared baseline echocardiographic parameters between groups. Left ventricular mass index and left atrium volume index were overall balanced between AL-CA and HHD group. All the groups fall under the category of preserved LVEF. The HHD group had higher LVEF (62.00 vs 59.00, P =0.005) and lower GLS (-20.12 vs -14.44, P <0.001) than the AL-CA group. E wave, A wave, and EA ratio were similar between AL-CA and HHD group. Lateral e' velocity was not significantly different between the two groups. Septal e' velocity was significantly higher in HHD group than that in AL-CA group (6.00 vs 4.00, P =0.002), and average E/e' was lower in HHD group (9.65 vs 13.04, P =0.026). Left atrial ejection fraction was significantly lower in AL-CA group than that in HHD group (48.50 vs 61.00, P <0.001).

Table 2. Baseline echocardiographic parameters

Factor	AL-CA	HHD	p-value	Control
	N=21	N=56	AL-CA vs HT	N=25
LVM, g	232.25 (32.47)	206.37 (62.46)	0.14	141.91 (25.84)
LVMI, g/m^2	128.75 (27.18)	114.74 (31.55)	0.068	73.96 (14.52)
IVS, mm	12.00 (2.00)	12.00 (1.00)	0.022	9.00 (2.00)
LVEDD, mm	47.90 (4.78)	49.64 (4.15)	0.12	47.48 (3.29)
LVPW, mm	12.00 (2.00)	11.00 (1.00)	<0.001	8.00 (1.00)
LVESD, mm	34.00 (4.00)	32.00 (4.50)	0.87	31.00 (3.00)
LVEF, %	59.00 (6.00)	62.00 (5.00)	0.005	64.00 (5.00)
GLS, %	-14.44 (4.05)	-20.12 (3.64)	<0.001	-22.59 (1.98)
E wave, cm/s	68.00 (37.00)	62.50 (18.00)	0.20	64.00 (14.00)
A wave, cm/s	79.20 (22.86)	81.02 (19.62)	0.73	72.68 (16.30)
EA ratio	0.81 (0.59)	0.80 (0.40)	0.12	0.90 (0.30)
Septal e' velocity, cm/s	4.00 (1.00)	6.00 (2.00)	0.002	8.10 (3.00)
Lateral e' velocity, cm/s	6.00 (2.00)	8.00 (3.00)	0.050	11.00 (3.00)
E/'e ratio	13.04 (9.93)	9.65 (4.30)	0.026	6.20 (1.60)
TR velocity, m/s	2.42 (0.43)	2.40 (0.29)	0.32	2.29 (0.16)
LA volume, ml	71.00 (25.00)	72.50 (23.00)	0.77	48.00 (14.00)
LAVI, (ml/m^2)	39.58 (16.74)	38.11 (11.72)	0.68	27.20 (6.48)
LAEF, %	48.50 (18.50)	61.00 (13.50)	<0.001	65.00 (11.00)

Note: LVM left ventricular mass, LVMI left ventricular mass index, IVS interventricular septum, LVEDD left ventricular end diastolic diameter, LVPW left ventricular posterior wall thickness, LVESD left ventricular end systolic diameter, LVEF left ventricular ejection fraction, GLS global longitudinal strain, TR velocity tricuspid regurgitant jet peak velocity, LAVI left atrium volume index, LAEF left atrial ejection fraction.

LA strain parameters

LA strain parameters were shown in Figure 2 and Table 3. Reduced LA strain was observed in both AL-CA group and HHD group. LASr and LASct were significantly lower (21.03 vs 26.17, P =0.01, and 12.11 vs 15.51, P=0.01, respectively) in AL-CA group than those in HHD group, while LAScd was not significantly different between the two groups (P=0.17). SD-TPS, SR-LAs, SR-LAe, and SR-LAa were similar between AL-CA group and HHD group. The cutoff values of LASr and LASct for discriminating between AL-CA and HHD were 19.53% and 11.34% according to ROC analysis, respectively. Correspondingly, the areas under the curve (AUCs) were 0.67, 95% CI [0.52–0.83] and 0.67, 95% CI [0.51–0.82], respectively (Figure 3).

Table 3. LA strain parameters

Factor	AL-CA	HHD	p-value	Control	p-value	p-value
	N=21	N=56	CA vs HHD	N=25	CA vs control	HHD vs control
LASr, %	21.03 (9.53)	26.17 (6.61)	0.01	39.71 (8.73)	<0.01	<0.01
LAScd, %	9.14 (5.01)	9.90 (6.64)	0.17	18.44 (7.37)	<0.01	<0.01
LASct, %	12.11 (6.48)	15.51 (4.24)	0.01	20.54 (4.77)	<0.01	<0.01
LASDTPS, %	8.85 (6.64)	6.60 (5.10)	0.27	4.12 (2.65)	<0.01	<0.01
SR-LAs, S^{-1}	1.14 (0.49)	1.24 (0.33)	0.28	1.79 (0.42)	<0.01	<0.01
SR-LAe, S^{-1}	-0.75 (0.24)	-0.82 (0.51)	0.66	-1.50 (0.67)	<0.01	<0.01
SR-LAa, S^{-1}	-1.61 (0.85)	-1.80 (0.46)	0.22	-2.62 (0.54)	<0.01	<0.01

LASr left atrium reservoir strain, LASct left atrium conduit strain, LAScd left atrium contraction strain, SD-TPS standard deviation of time to peak positive strain, SR-LAs peak systolic strain rate, SR-LAe early diastolic strain rate, SR-LAa late diastolic strain rate

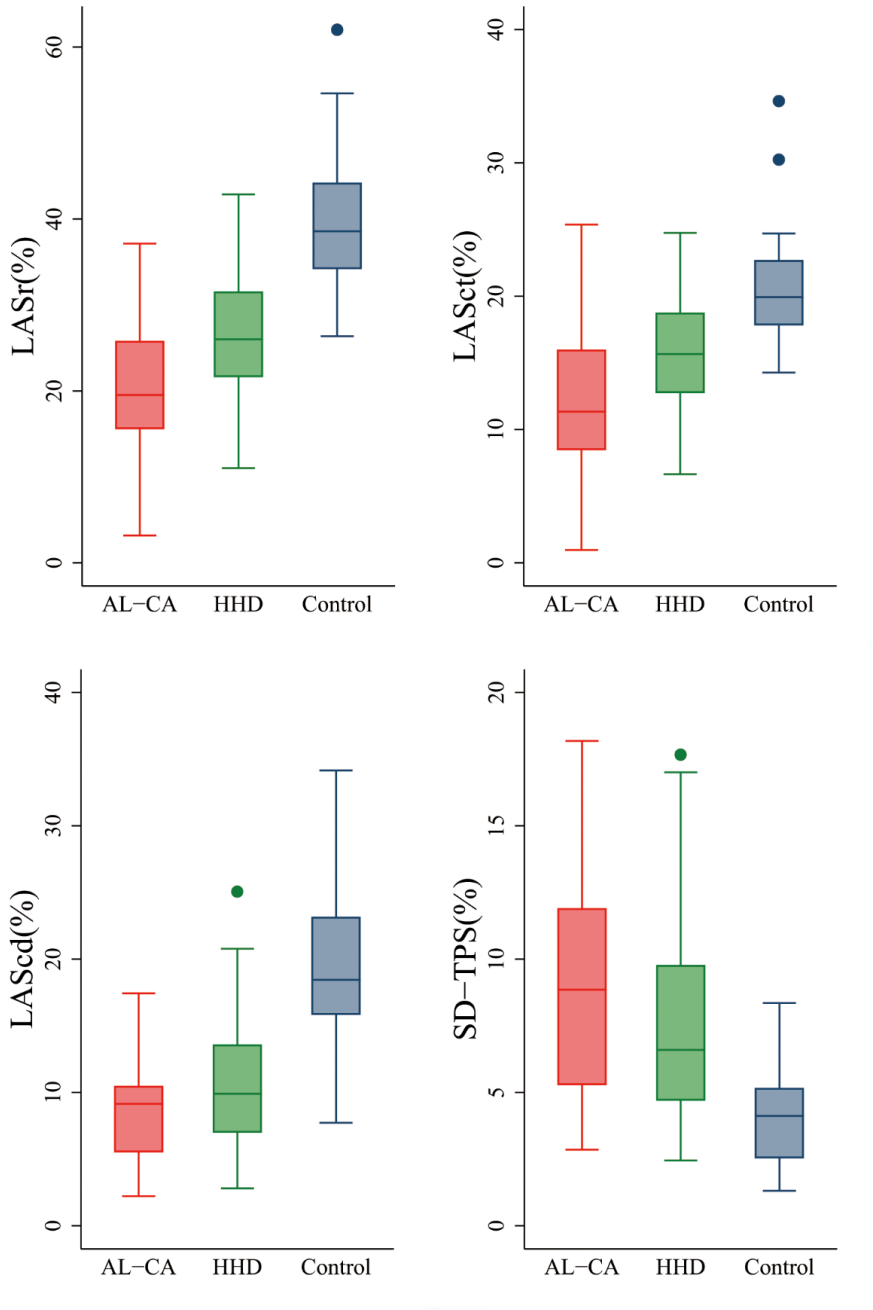

Figure 2. Box plots of LASr, LASct, LAScd, and SD-TPS in AL-CA, HHD, and control group.

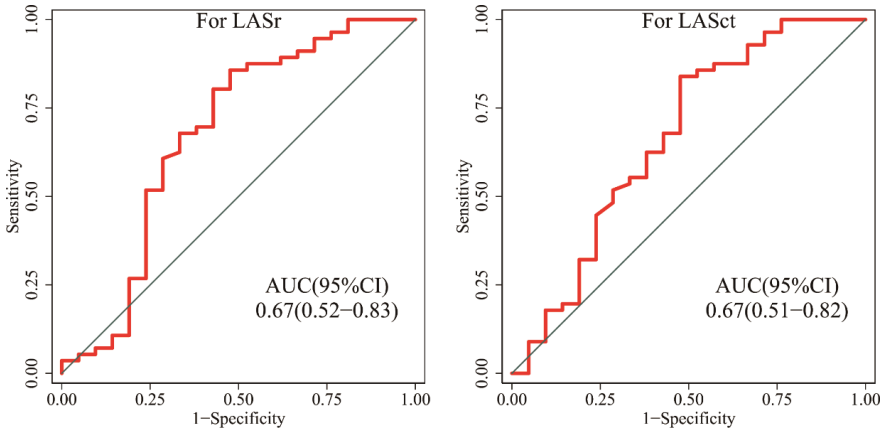

Figure 3. ROC curve of LASr for discriminating AL-CA from HHD

Correlation between LA strain and LV structure, LV function, and LA size

Overall, in AL-CA group, LA reservoir, conduit and pump functions were correlated with LV function and LAVI (Table 4). In HHD group, weak correlations between LA strain and LV function were observed. LVGLS was correlated with LASr (r=-0.84, P<0.01), LAScd (r=-0.63, P<0.01), and LASct (r=-0.83, P<0.01) in AL-CA group. Correlations between E/e' and LASr (r=-0.84, P<0.01), LAScd (r=-0.63, P<0.01), and LASct (r=-0.83, P<0.01) were also observed in AL-CA group.

Table 4. Correlation between LA strain and LV structure, LV function, and LA size

Variables		In patients with AL-CA
		LASr
Left ventricular structure and function	Left ventricular structure and function	Left ventricular structure and function
LVMI		-0.34(P=0.12)
LVGLS		-0.84(P<0.01)
LVEF		0.58(P=0.01)
E wave		-0.57(P=0.01)
A wave		0.47(P=0.04)
E/e'		-0.74(P<0.01)
Left atrial size	Left atrial size	Left atrial size
LAVI		-0.55(P=0.01)

Discussion

The main findings in the current study were as follows: (a) LA strain parameters were significantly reduced in both AL-CA and HHD group; (b) Patients with AL-CA had reduced LASr and LASct compared with those with HHD, and (c) LAScd and SD-TPS were similar between AL-CA and HHD group.

In the current study, we showed lower IVS and LVPW thickness than that in previous studies[9,10,19]. It suggests that patients enrolled in the current study had less severe disease progression than those in previous studies. Similar to the previous study, all LA strain parameters were severely impaired in AL-CA and HHD group[9]. LA strain has recently emerged as a powerful assessment in evaluation of left ventricular diastolic dysfunction[20].Our previous study showed that LASr was an independent predictor of elevated left ventricular end-diastolic pressure[21]. In the current study, higher E/e' values correlated with decreased LASr in AL-CA group and HHD group, which suggesting a decreased diastolic function. Gan et al. demonstrated that LA remodeling reflected by larger LAVI had an incremental negative association with LASr in patients without

prior cardiac disease[22]. In the current study, LA stain parameters negatively correlated with LAVI in patients with AL-CA and patients with HHD, which was consistent with prior study[22].

Compared with those with HHD, patients with AL-CA had significantly lower LASr and LASct in the current study. Karen et al. also showed a significant reduction of LASr and LASct in patients with AL-CA compared with those with HHD [9]. In AL-CA group, amyloid infiltration into the LA wall may lead to a marked functional deterioration of this thin-walled and very vulnerable structure, and that these alterations may lead to a significant decrease in LA reservoir and pump function. In the current study, higher LA strain values consisted with lower left ventricular thickness than that in previous studies[9,10,19].

Notably, the difference in LAScd between AL-CA group and HHD group was not significant in the current study. Kotaro et al. also showed that conduit function of LA was not impaired in all the three aetiologies of CA[10]. A possible mechanism is that LA volume changes (conduit function) may be a compensatory mechanism when LA reservoir and pump function are impaired.

LA structural and functional remodeling are associated with AF[23,24]. Kawakami et al. showed that SD-TPS is an independent predictor of new-onset atrial fibrillation (AF) and correlated with LASr[18]. In order to assess LA strain parameters properly, we excluded patients with AF. Both AL-CA group and HHD group had increased SD-TPS. However, the difference was not significant between the two groups. We hypothesized that the risk of AF was no increased in the early stage of amyloid infiltration, although reservoir and pump function of LA were severely impaired.

Study limitations

There are several limitations to the current study. First, patients with AF were excluded. Typical of AF is LA remodeling. Reactive deposition of collagen fibers in the interstitium causes massive fibrosis, and an inverse relationship exists between the grade of fibrosis and LA strain[25,26]. As a case-control study, the duration of AF was not available. As a result, LA strain in CA patients with AF should be investigated separately. Second, a specific software for evaluating LA strain by speckle-tracking is not yet available. Therefore, we analyzed LA strain using software for evaluating the left ventricle. Third, this is a single-centered study enrolling AL-CA and HHD patients. Therefore, our findings warrant further confirmation from different centers and in different cardiac amyloidosis populations.

Conclusions

AL-CA patients had marked reductions in LASr and LASct. LA strain may be helpful in differentiating AL-CA from HHD patients.

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