Cardiovascular Ultrasound

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Determinants of left atrial reservoir strain and diagnostic potential for cardiac amyloidosis in pathological left ventricular hypertrophy

Katsuji Inoue[1,2*], Yasuhisa Nakao[2], Makoto Saito[3], Masaki Kinoshita[3], Haruhiko Higashi[2] and Osamu Yamaguchi[2]

Abstract

Background Left ventricular (LV) long-axis shortening at the cardiac base is a determinant of left atrial (LA) reservoir function. Cardiac amyloidosis (CA) is characteristic of amyloid deposition predominantly in the LV basal wall. We investigated the relationship between LV basal strain and LA reservoir strain among patients with pathological LV hypertrophy and subsequently evaluated the diagnostic ability of LA reservoir strain to identify CA etiology and its predictive value for heart failure hospitalization.

Methods We retrospectively analyzed 341 patients with LV hypertrophy. Cardiac etiologies were diagnosed by tissue biopsy, cardiac magnetic resonance imaging or ^{99m}Tc-PYP scintigraphy. LV basal strain and LA reservoir strain were analyzed.

Results Patients were diagnosed with CA (n = 75) and other etiologies (n = 266). LV basal strain was correlated with LA reservoir strain in the CA group ($r = 0.58$, $p < 0.01$) and the non-CA group ($r = 0.44$, $p < 0.01$). A binary logistic regression analysis showed that relative apical sparing of longitudinal strain, septal E/e' and LA reservoir strain had the ability to discriminate between the CA and non-CA groups ($p < 0.01$ for all). The area under the curve for relative apical sparing of longitudinal strain had a stronger ability than LA reservoir strain to discriminate CA from non-CA etiologies (0.90 versus 0.81, respectively; $p < 0.01$). During the follow-up period (median 2.7 years), the incidence of heart failure hospitalization was higher in the CA group than the non-CA group (35% versus 14%, respectively; $p < 0.01$). According to univariate Cox regression analysis, three LA factors (LA reservoir strain, E/e' and LA volume index) were associated with heart failure hospitalization in the non-CA group ($p < 0.05$ for all).

Conclusions LA reservoir strain was associated with LV basal strain among patients with pathological LV hypertrophy. Echocardiographic assessment of LA reservoir strain might add diagnostic value to identify CA etiology in these patients.

Keywords Echocardiography, Cardiac amyloidosis, Left ventricular hypertrophy, Left atrial reservoir strain, Left ventricular basal strain

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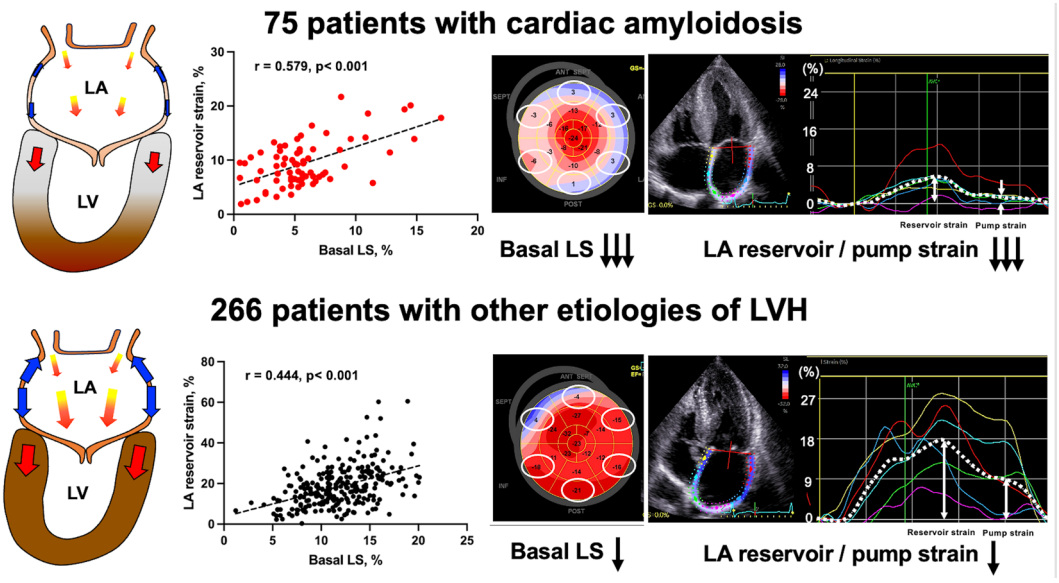
Graphical Abstract



Background

Left ventricular (LV) hypertrophy (LVH) is a form of structural remodeling known as a robust risk factor for heart failure occurrence [1]. Increased LV wall thickness is caused by myocardial histological changes, including myocyte cellular hypertrophy, interstitial fibrosis or depositions of abnormal proteins, such as amyloid fibrils. LV wall thickening leads to abnormal LV diastolic properties, such as delayed relaxation and increased chamber stiffness [2, 3].

Echocardiography is a first-line tool to diagnose patients with LVH noninvasively in clinical practice. It enables estimation of LV wall thickness as well as the severity of diastolic dysfunction [4, 5]. Despite preservation of the LV ejection fraction (EF), myocardial longitudinal shortening is impaired in patients with pathological LVH. LV global longitudinal strain (GLS) by speckle tracking echocardiography (STE) enables detection of subclinical LV systolic dysfunction earlier than measurement of the LVEF in patients with LVH [6]. Among patients with LVH, a characteristic 'apical sparing pattern' of LV longitudinal strain on STE is a potential echocardiographic sign of cardiac amyloidosis (CA) etiology [7]. The 'apical sparing pattern' is a strain distribution in which LV strain at the basal wall is reduced despite preserved LV strain at the apex. Previously, Barbier and colleagues reported that LV basal descent, produced by LV long-axis shortening, was a major determinant of left atrial (LA) reservoir function [8]. LA reservoir function is markedly reduced in patients with CA [9].

We hypothesized that LA reservoir strain was associated with LV basal strain, particularly in patients with CA. Accordingly, we investigated the association between LV basal strain and LA reservoir strain in patients with pathological LVH and evaluated the diagnostic ability of LA reservoir strain to identify CA etiology and its predictive value for heart failure hospitalization.

Methods

Study population

We retrospectively enrolled 341 patients with LVH at Ehime University and Kitaishikai Hospital from March 2006 to November 2022. Patients with acute myocardial infarction and severe aortic stenosis were excluded. All patients underwent echocardiography, with which LVH was diagnosed when mean LV wall thickness was >10 mm (men) and >9 mm (women) based on upper limit of normal values of wall thickness [4, 10]. Furthermore, a detailed examination by cardiac magnetic resonance imaging (CMR), ^{99m}Tc-PYP scintigraphy or tissue biopsy was carried out for diagnosing cardiac disease etiology based on guidelines for cardiomyopathy from the European Society of Cardiology and Japanese Society of Cardiology [11, 12]. CA was confirmed by endocardial biopsy or extracardiac biopsy in the absence of an alternative cause for increased LV wall thickness [13]. In particular, transthyretin cardiac amyloidosis (ATTR) was diagnosed noninvasively from evidence of Grade 2 or 3 myocardial uptake on ^{99m}Tc-PYP scintigraphy, which was confirmed by radiologists. Amyloid light-chain cardiac amyloidosis (AL) was diagnosed by a positive hematologic test of immunoglobulin light chains, which was confirmed by hematologists. This study was conducted in accordance with the Declaration of Helsinki

and approved by the ethics committee of Ehime University Graduate School of Medicine (approval numbers: 1803003 and 1905015), and it was performed using the opt-out method of our hospital websites.

Echocardiography

Comprehensive echocardiographic examinations were performed using GE Vivid E9 or E95 (Vivid E9 or Vivid E95; GE Vingmed, Horten, Norway). Conventional echocardiographic parameters were analyzed as recommended by the American Society of Echocardiography [4]. To evaluate LA and LV longitudinal function, STE was conducted after careful acquisition of non-foreshortened images in both the LA and LV chambers. LA and LV strain were calculated with dedicated software (EchoPAC PC BT13: GE Healthcare). LA strain was measured for an apical 4-chamber view based on the consensus document of the EACVI/ASE/Industry Task Force [14]. The two components of LA strain, LA reservoir strain and LA pump strain, were analyzed with the zero-strain reference at end-diastole. LV strain was estimated segmentally and globally in the three standard apical views. In terms of segmental LV strain analysis, LV segmental strain was calculated separately in the basal, mid and apical layers, and LV basal, mid and apical strain were estimated as the average value in each layer. LV global strain was also estimated as the average value in all segments [4].

Outcome

The outcome was defined as hospital admission for unexpected heart failure after the echocardiographic examination.

Statistics

Categorical variables were expressed as number and percentage and the comparison of variables between the CA and non-CA groups was analyzed with the χ^2 test. Continuous variables were expressed as median value and interquartile range (IQR), and comparative analysis was performed with the Mann-Whitney U test. Linear regression analysis was performed to investigate the relationship of LV segmental strain with LA reservoir strain. Multivariate regression analyses were used to find the determinants of LA reservoir strain among echocardiographic parameters. We used a binary logistic regression model, as well as a receiver operating characteristic (ROC) curve analysis for differentiating CA etiology from non-CA etiologies. Univariate Cox regression analysis was performed to identify variables significantly associated with outcome. The Kaplan-Meier method and log-rank test were used to examine the event rates of heart failure hospitalization during the follow-up period. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [15] and GraphPad Prism version 10.2.2 (Boston, Massachusetts, USA).

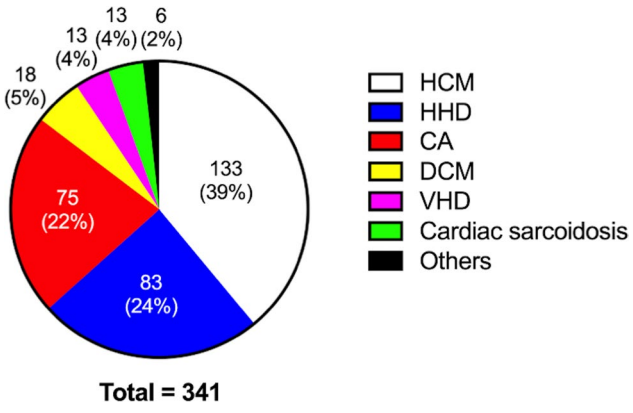


Fig. 1 Cardiac etiologies of left ventricular wall thickening. HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; CA, cardiac amyloidosis; DCM, dilated cardiomyopathy; VHD, valvular heart disease

Results

Baseline characteristics

Among the 341 enrolled patients, 133 (39%) were diagnosed with hypertrophic cardiomyopathy (HCM), 83 (24%) with hypertensive heart disease, 75 (22%) with CA, and the remaining 50 with other etiologies (Fig. 1). Among the 75 patients with CA, 43 patients were diagnoses with ATTR subtype by histological confirmation (endocardial biopsy: $n=20$, extracardiac tissue biopsy: $n=3$) or imaging (^{99m}Tc-PYP scintigraphy: $n=20$). 24 patients were diagnosed with AL subtype (endocardial biopsy: $n=17$, extracardiac tissue biopsy: $n=7$). The remaining 8 patients were histologically diagnosed with CA by Congo red staining with conventional light microscopy (endocardial biopsy: $n=7$, extracardiac tissue biopsy: $n=1$), however, the CA subtypes were not undetermined, because specific amyloid typing had not been conducted in the early part of this study.

Table 1 shows the characteristics of the patients in this study. Age and male gender were higher in the CA group than in the non-CA group. Systolic and diastolic blood pressure were lower, and heart rate was higher in the CA group than in the non-CA group. There was no significant difference in the incidence of atrial fibrillation between groups. In terms of medical treatment, β blocker, mineralocorticoid receptor antagonist and loop diuretic use were higher in the CA group than in the non-CA group. The estimated glomerular filtration rate (eGFR) and serum levels of hemoglobin, albumin and sodium were lower, while the levels of B-type natriuretic peptides were higher in the CA group than in the non-CA group.

Table 1 Patient characteristics

Variables	Overall	Non-CA group	CA group	*p* value*
	(*n* = 341)	(*n* = 266)	(*n* = 75)	
Clinical variables				
Age, years	68 [56–76]	66 [55–73]	76 [72–83]	< 0.01
Male sex, n [%]	218 [64]	156 [59]	62 [83]	< 0.01
BMI, kg/m^2	23.6 [21.0-26.7]	24.0 [21.4–27.2]	22.0 [20.2–24.5]	< 0.01
BSA, m^2	1.63 [1.51–1.78]	1.65 [1.51–1.82]	1.58 [1.47–1.68]	< 0.01
Systolic BP, mmHg	130 [113–143]	132 [118–148]	112 [98–134]	< 0.01
Diastolic BP, mmHg	71 [62–81]	73 [65–82]	62 [55–75]	< 0.01
Heart rate, bpm	67 [60–77]	65 [58–76]	74 [66–83]	0.01
AF, n [%]	83 [24]	61 [23]	22 [29]	0.25
Paroxysmal type	54 [16]	38 [14]	16 [21]	
Permanent type	29 [9]	23 [9]	6 [8]	
Medications, n, %				
β blocker	179 [52]	155 [58]	24 [32]	< 0.01
ACEi/ARB	151 [44]	118 [44]	33 [44]	0.96
MRA	80 [23]	54 [20]	26 [35]	0.01
Loop diuretics	128 [38]	74 [28]	54 [72]	< 0.01
Serum markers				
Hemoglobin, g/dL	13.4 [11.9–14.7]	13.5 [12.1–14.9]	12.6 [11.4–14.1]	0.01
eGFR, mL/min/1.73 m^2	60.5 [45.9–73.4]	62.5 [49.1–74.4]	46.5 [40.8–61.6]	< 0.01
Albumin, mg/L	4.0 [3.6–4.3]	4.1 [3.7–4.3]	3.8 [3.3–4.1]	< 0.01
Sodium, mmol/L	140 [139–142]	140 [139–142]	139 [137–141]	< 0.01
BNP, pg/mL	146 [59–369]	111 [45–269]	290 [162–628]	< 0.01

Values are median [interquartile range] or number [percentage]. CA, cardiac amyloidosis; BMI, body mass index; BSA, body surface area; BP, blood pressure; AF, atrial fibrillation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide. *Non-CA group versus CA group

Conventional echocardiographic parameters

Conventional echocardiographic findings are shown in Table 2. LV wall thickness, especially posterior wall thickness, was greater in the CA group than in the non-CA group. The LVEF was reduced, and LV diastolic functional parameters (mitral E/A ratio, septal e' and septal E/e') were deteriorated in the CA group compared with those in the non-CA group. The LA volume index (LAVi) was larger, and the tricuspid regurgitation velocity was higher in the CA group than in the non-CA group.

Left ventricular and atrial strain parameters

LV and LA strain profiles are shown in Table 3; Fig. 2. Feasibilities to acquire LA reservoir strains (95%) were higher than LA pump strain (86%). LV global longitudinal strain (GLS) was reduced in the CA group compared with that in the non-CA group. In the segmental analyses of LV strain, LV basal and mid longitudinal strains were reduced in the CA group compared with those in the non-CA group. Conversely, LV apical strain was significantly increased in the CA group compared with that in the non-CA group. LA reservoir and pump strains were markedly reduced in the CA group compared with those in the non-CA group. As shown in Fig. 3, LV basal strain was significantly correlated with LA reservoir strain in both the CA and non-CA groups. The correlation coefficient was relatively higher in the CA group than that in the non-CA group. Table 4 shows the results of the multivariate analysis for the determinants of LA reservoir strain in two separate models, in which either GLS or LV basal strain was included. In the non-CA group, the presence of atrial fibrillation and LV basal strain were independently associated with LA reservoir strain. In the CA group, mitral E/A ratio and LV basal strain were independently associated with LA reservoir strain.

Discrimination of CA etiology from other etiologies by echocardiographic parameters

Figure 4 shows the ROC curves that differentiate the CA group from the non-CA group by echocardiographic parameters. In terms of LV factors, the AUC values of relative apical LS, basal LS and apical LS were 0.90, 0.89, and 0.58, respectively. In terms of LA factors, LA reservoir strain, E/e' and LAVi to differentiate between the CA and non-CA groups were 0.81, 0.76 and 0.65, respectively. The AUC values of relative apical LS and basal LS were significantly higher than that of LA reservoir strain ($p < 0.01$), while the AUC value of LA reservoir strain was significantly higher than that of the LAVi ($p < 0.01$). The cut-off value of relative apical LS (0.83) had 82% sensitivity and 81% specificity, while that of LA reservoir strain (12%) identified the CA group with 76% sensitivity and 73% specificity.

As shown in Table 5, a binary logistic regression analysis found that relative apical LS, E/e' and LA reservoir strain had the ability to discriminate between the CA group and the non-CA group ($p < 0.01$ for all).

Outcome

During the follow-up period (median 2.7 years, IQR 281–2223 days), heart failure hospitalization occurred in 26 patients (35%) with CA and 38 patients (14%) with non-CA etiologies. Regarding to the periods from echocardiographic examination to the onset of heart failure, the median and IQR values in CA group were 1.2 years and 109–1117 days, while the median and IQR values in non-CA group were 3.7 years and 537–2733 days. The incidence of heart failure hospitalization was greater in the CA group than in the non-CA-group ($p < 0.01$). Kaplan-Meier analysis showed that the rate of heart failure

Table 2 Conventional echocardiographic parameters

Variables	Overall (*n* = 341)	Non-CA group (*n* = 266)	CA group (*n* = 75)	*p* value *
IVST, mm	13 [11–15]	12 [11–15]	14 [12–16]	0.25
PWT, mm	11 [10–13]	11 [10–12]	13 [11–15]	< 0.01
Mean LVWT, mm	12 [11–14]	12 [11–13]	14 [12–15]	< 0.01
LVEF, %	59 [48–67]	61 [49–67]	53 [44–61]	< 0.01
LVEDV, mL	73 [57–98]	74 [59–106]	69 [53–81]	< 0.01
LVESV, mL	29 [20–45]	29 [20–48]	323 [22–41]	0.07
LV mass index, g/m^2	138 [116–171]	137 [115–167]	145 [123–203]	< 0.05
E velocity, cm/s	66 [54–83]	63 [52–82]	76 [66–90]	0.04
A velocity, cm/s	68 [50–88]	72 [54–91]	56 [36–71]	< 0.01
E/A	0.9 [0.7–1.4]	0.8 [0.7–1.2]	1.4 [0.8–2.1]	< 0.01
E-wave DcT, ms	208 [167–254]	213 [170–259]	180 [152–208]	< 0.01
Septal e', cm/s	4 [3–6]	4 [4–6]	3 [3–4]	< 0.01
Septal E/e'	15 [12–22]	14 [11–19]	22 [16–28]	< 0.01
LAVi, mL/m^2	43 [31–55]	41 [30–53]	50 [40–59]	< 0.01
TR velocity, m/s	2.4 [2.1–2.7]	2.3 [2.0-2.7]	2.5 [2.2–2.8]	0.02
MR grade, n (%) mild/moderate/severe	188/35/9 (55/10/3)	148/23/8 (56/9/3)	40/12/1 (53/16/1)	0.17

Values are median [interquartile range] or number [percentage]. CA, cardiac amyloidosis; IVST, Interventricular septal wall thickness; PWT, LV posterior wall thickness; LV, left ventricular; WT, wall thickness; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; DcT, deceleration time; LAVi, left atrial volume index; TR, tricuspid regurgitation; MR, mitral regurgitation. *Non-CA group versus CA group

Table 3 LV and LA strain parameters

Variables	Available data *n* (%)	Non-CA group (*n* = 266)	Available data *n* (%)	CA group (*n* = 75)	*p* value *
LV strains, %					
GLS	261 (98)	13 [10–16]	74 (99)	10 [8–12]	< 0.01
Basal LS	261 (98)	12 [9–14]	74 (99)	5 [4–7]	< 0.01
Mid LS	261 (98)	12 [9–15]	74 (99)	9 [7–12]	< 0.01
Apical LS	261 (98)	15 [10–20]	74 (99)	15 [13–19]	0.02
LA strains, %					
Reservoir strain	253 (95)	18 [12–24]	71 (95)	9 [6–12]	< 0.01
Pump strain	228 (86)	10 [6–13]	58 (77)	3 [2–7]	< 0.01

Values are median [interquartile range] or number [percentage]. LV, left ventricular; LA, left atrial; CA, cardiac amyloidosis; GLS, global longitudinal strain; LS, longitudinal strain. *Non-CA group versus CA group

hospitalization was higher in the CA group than in the non-CA group (Supplementary Fig. 2).

According to univariate Cox regression analysis (Table 6), atrial fibrillation, hemoglobin, albumin and BNP were associated with heart failure hospitalization in the non-CA group. Furthermore, three LA factors (LA reservoir strain, E/e', and LAVi) were associated with heart failure hospitalization. In the non-CA group, Kaplan-Meier analysis stratified by abnormal values of LA reservoir strain (< 18%) and GLS (< 16%) [16, 17] showed that patients with LA reservoir strain < 18% were at higher risk for heart failure hospitalization than those with LA strain ≥ 18% ($p < 0.01$), while there was no significant difference in heart failure hospitalization between patients with GLS < 16% and those with GLS ≥ 16% ($p = 0.12$) (Fig. 5).

There were no significant correlations of clinical and echocardiographic parameters with heart failure hospitalization in the CA group.

Discussion

First, this study demonstrated that LA reservoir strain was significantly associated with LV longitudinal strain in the cardiac base, especially in patients with CA etiology. Second, LA reservoir strain had additive value to relative apical LS for discriminating patients with CA etiology among patients with pathological LVH. Third, reduced LA reservoir strain at baseline was associated with heart failure hospitalization in patients with LVH with non-CA etiologies.

LVH is a typical form of structural remodeling in patients with heart failure with preserved ejection fraction (HFpEF). Echocardiography is a first-choice imaging modality to identify patients with LVH, thus facilitating the diagnosis of cardiac etiologies by multimodal cardiac analysis, such as cardiac magnetic resonance imaging, scintigraphy, and tissue biopsy. A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) emphasizes consideration of an etiological workup by multimodal imaging to identify specific HFpEF etiologies for advancing the field of targeted therapies [18].

LA dilatation is a consequence of longstanding LV diastolic dysfunction and elevated LV filling pressure [19]. LA dilatation coexists with LA functional impairment.

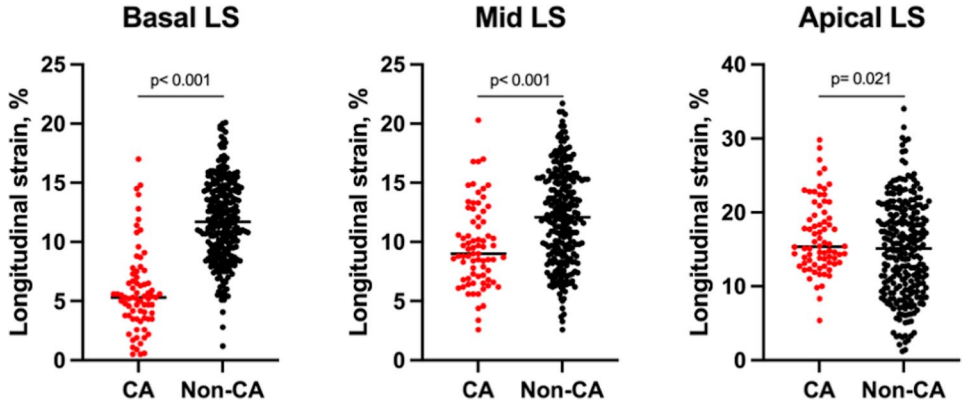


Fig. 2 Comparisons of longitudinal strains in the basal, mid- and apical segments of the left ventricle between the CA and non-CA groups. Longitudinal strains in the basal and mid-segments were significantly lower in the CA group than in the non-CA group, although there was no significant difference in longitudinal strain in the apical segment between groups. LS, longitudinal strain; CA, cardiac amyloidosis

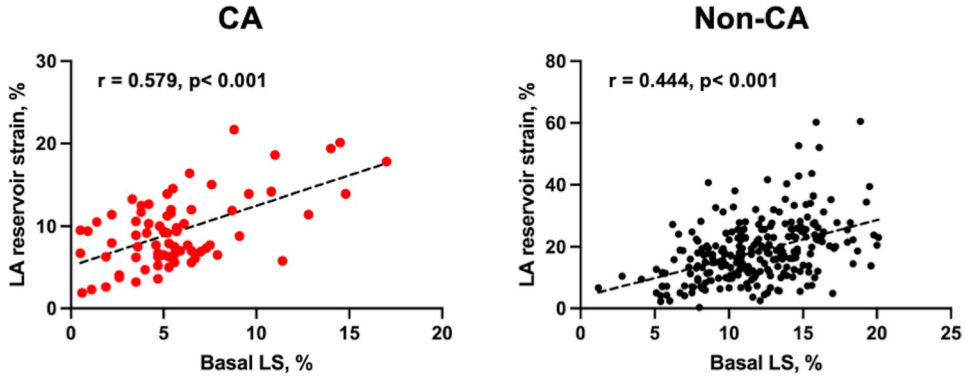


Fig. 3 Correlation of left ventricular longitudinal strain at the basal segment with left atrial reservoir strain. There were significant correlations between left ventricular longitudinal strain at the basal segment with LA reservoir strain in both the CA and non-CA groups. LS, longitudinal strain; CA, cardiac amyloidosis; LA, left atrial

Table 4 Determinants of LA reservoir strain in multivariate regression analysis

Variables	Non-CA group (*n* = 266)				CA group (*n* = 75)			
	Model 1		Model 2		Model 1		Model 2	
	β	p value	β	p value	β	p value	β	p value
Atrial fibrillation	-0.14	0.02	-0.14	0.03	-0.18	0.18	-0.17	0.15
LVEF	0.04	0.59	0.04	0.55	0.22	0.16	0.14	0.31
LV mass index	-0.06	0.39	-0.04	0.56	-0.01	0.93	0.05	0.73
E/A	-0.07	0.25	-0.08	0.17	-0.31	0.02	-0.25	< 0.05
Septal E/e'	0.01	0.92	0.02	0.8	-0.09	0.52	-0.08	0.53
LAVi	-0.15	0.18	-0.17	< 0.01	-0.04	0.76	-0.07	0.58
GLS	0.32	< 0.01			0.14	0.36		
Basal LS			0.35	< 0.01			0.34	0.02

LA, left atrial; CA, cardiac amyloidosis; β, standardized regression coefficient; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index; GLS, global longitudinal strain; LS, longitudinal strain. Either GLS or basal LS was included in model 1 and model 2 of multivariate analysis

LA strain, in particular, reservoir strain, has emerged as a diagnostic parameter for assessing LV diastolic function and filling pressure in patients with suspected heart failure [20, 21]. Our previous study revealed that LA reservoir strain was determined mainly by LV longitudinal strain in patients with preserved LVEF [22]. Furthermore, a study by Barbier and colleagues reported that LV long-axis shortening at the cardiac base was an important determinant of LA reservoir function [8]. In our study, we demonstrated that there was a close relationship between LV basal strain and LA reservoir strain in patients with pathological LVH. We conducted an

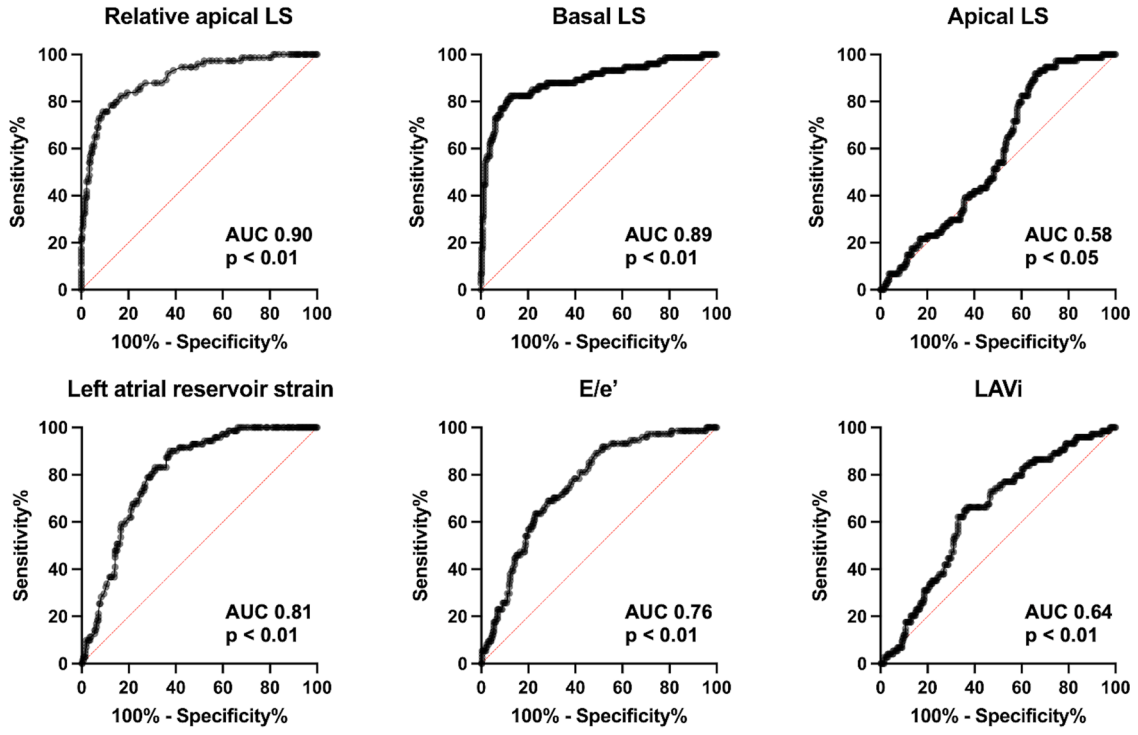


Fig. 4 ROC curves for identification of CA etiology by echocardiographic factors. The AUC values of relative apical LS, basal LS, apical LS, LA reservoir strain, E/e' and LAVi to differentiate between the CA and non-CA groups were 0.90, 0.89, 0.58, 0.81, 0.76 and 0.65, respectively. The AUC value of relative apical LS was significantly higher than that of LA reservoir strain ($p < 0.01$), while the AUC value of LA reservoir strain was significantly higher than that of the LAVi ($p < 0.01$). ROC, receiver operating characteristic; CA, cardiac amyloidosis; LS, longitudinal strain; LA, left atrial; LAVi, left atrial volume index; AUC, area under the curve

Table 5 Binary logistic regression analysis to discriminate CA group from non-CA group

Variables	Odds ratio	95%CI	*p* value
Relative apical LS	0.03	0.01–0.08	< 0.01
LAVi	1	0.99–1.02	0.58
Septal E/e'	0.94	0.90–0.98	< 0.01
LA reservoir strain	1.14	1.06–1.22	< 0.01

CI, confidence interval; LS, longitudinal strain; LAVi, left atrial volume index; LA, left atrial

etiological workup by multimodal imaging in all patients with LVH, and 22% were diagnosed with a CA etiology. The association between LV basal strain and LA reservoir strain was strong, particularly in patients with CA compared with patients with other LVH etiologies. Abnormal amyloid proteins deposit predominantly in the basal layer of the left ventricle [23], which could limit the descent of the mitral valve plane and restrict LA reservoir function.

Our study also demonstrated that LA reservoir strain could differentiate CA etiology from other LVH etiologies with moderate accuracy, although relative apical LS had the best accuracy to discriminate CA etiology among echocardiographic parameters. These results were inconsistent with a previous report showing a higher diagnostic accuracy of LA reservoir strain than relative apical LS in discriminating CA etiology in 54 patients with unknow LVH etiologies [24]. Although our study enrolled a relatively large number of patients with LVH ($n = 341$), we enrolled patients with less severe LVH (mean LV wall thickness, 12 mm) than the previous investigation (mean LV wall thickness, 17 mm). The differences in background characteristics and pathophysiological stage in LVH might lead to inconsistent results in the ability of LA reservoir strain and relative apical LS to diagnose patients with CA. Our study also showed that LV basal strain had good accuracy, similar to relative apical LS, in distinguishing CA etiology from other LVH etiologies. The diagnostic potential of LA reservoir strain for CA etiology might be explained by a pathophysiological link between LV basal shortening and LA reservoir function in patients with CA.

LA reservoir function is also determined by LA stiffness [8]. Amyloid deposition is possibly advanced in the left atrium. Our previous study with cardiac magnetic resonance imaging showed that late gadolinium enhancement was present in most patients with CA [25]. LA involvement of abnormal amyloid proteins could induce LA chamber stiffening, resulting in further deterioration of LA reservoir capacity in patients with CA.

Table 6 Univariate Cox regression analysis for HF hospitalization

Variables	Non-CA group	CA group
	(*n* = 266)	(*n* = 75)
Clinical parameters	HR [95%CI]	HR [95%CI]
Age	1.02 [0.99–1.04], *p* = 0.26	1.01 [0.97–1.05], *p* = 0.58
Male gender	0.73 [0.38–1.38], *p* = 0.33	1.26 [0.37–4.27], *p* = 0.71
Systolic blood pressure	1.00 [0.98–1.01], *p* = 0.61	0.99 [0.97-1.00], *p* = 0.12
Atrial fibrillation	4.36 [2.29–8.28], *p* < 0.01	0.80 [0.30–2.16], *p* = 0.66
Hemoglobin	0.83 [0.71–0.98], *p* = 0.03	0.93 [0.74–1.17], *p* = 0.54
Albumin	0.35 [0.20–0.61], *p* < 0.01	0.86 [0.49–1.50], *p* = 0.60
eGFR	0.99 [0.97-1.00], *p* = 0.08	1.00 [0.98–1.01], *p* = 0.90
BNP	1.00 [1.00–1.00], *p* < 0.01	1.00 [1.00–1.00], *p* = 0.29
Echocardiographic parameters		
LVEF	0.99 [0.97–1.02], *p* = 0.52	1.00 [0.97–1.04], *p* = 0.98
LVGLS	0.92 [0.84–0.99], *p* = 0.03	1.01 [0.90–1.13], *p* = 0.84
Mitral E/A ratio	1.62 [1.01–2.62], *p* < 0.05	1.23 [0.88–1.72], *p* = 0.23
Septal E/e'	1.04 [1.01–1.08], *p* < 0.01	1.04 [1.00-1.08], *p* = 0.07
LAVi	1.01 [1.00-1.02], *p* < 0.01	1.01 [0.99–1.03], *p* = 0.42
LA reservoir strain	0.94 [0.90–0.98], *p* < 0.01	1.01 [0.93–1.10], *p* = 0.82
LA pump strain	0.95 [0.88–1.02], *p* = 0.18	0.97 [0.84–1.12], *p* = 0.66

Values are median [interquartile range] or number [percentage]. HF, heart failure; CA, cardiac amyloidosis; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LAVi, left atrial volume index

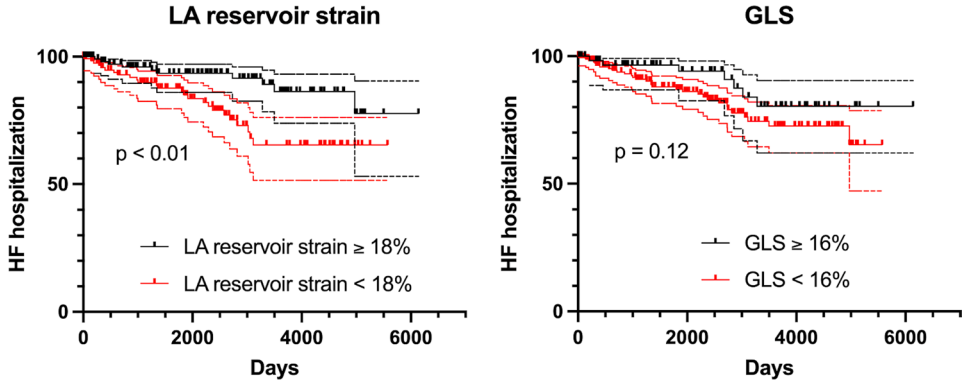


Fig. 5 Kaplan-Meier analysis of time to heart failure hospitalization based on LA reservoir strain and GLS in the non-CA group. HF, heart failure; LA, left atrial; GLS, left ventricular global longitudinal strain; CA, cardiac amyloidosis.

LA pump function was extremely reduced in patients with CA. The reduction in LA pump strain could reflect LA myopathy in patients with CA, even in sinus rhythm. As shown in supplementary Fig. 1, LA pump strain (6%) could discriminate patients with CA from those without CA with 72% sensitivity and 78% specificity. LA pump strain is a potential marker of LA intrinsic function; however, the feasibility of the acquisition of LA pump strain was relatively low (86%) compared with that of LA reservoir strain (95%). Toma et al. previously reported that LA relaxation at the early reservoir phase was closely associated with LA pump function [26]. LA myopathy might be a mechanism of LA reservoir function deterioration via atrial contraction-relaxation coupling in patients with CA. LA reservoir strain was influenced by LV longitudinal mechanics in the cardiac base and LA intrinsic factors, such as LA stiffening and myopathy, thus enabling identification of CA etiology in patients with pathological LVH.

The presence of LVH with LA remodeling is closely linked to heart failure occurrence [27]. This study also demonstrated that three LA echocardiographic parameters (LA reservoir strain, E/e' and LAVi) were associated with an increased incidence of heart failure hospitalization in 266 patients in the non-CA group. In particular, the cut-off value of LA reservoir strain (18%) could discriminate patients at high risk of heart failure hospitalization beyond the cut-off value of GLS (16%), which was an established predictive marker for heart failure hospitalization in patients with HFpEF [28]. These findings could inform the importance of LA reservoir function

for preventing the onset of heart failure in patients with pathological LVH.

In this study, despite their limited number ($n=75$), patients with CA experienced higher rates of heart failure hospitalization than those with other LVH etiologies (supplementary Fig. 2). It is well known that patients with CA are prone to develop heart failure due to advanced LV diastolic dysfunction, LA myopathy and atrial arrhythmias [29]. LA reservoir strain could have additive value to relative apical LS for distinguishing patients with CA from those with other LVH etiologies, facilitating the conduct of multimodal imaging for etiological workup and introduction of therapeutic options in patients with CA.

Limitations

This study had several limitations. First, 8 of 75 patients (11%) with CA were not assessed for AL and ATTR subtypes. Second, some patients in the non-CA group, such as those with HCM or cardiac sarcoidosis, had heterogenous LV wall thickness, which could have influenced the scatter plots regarding the association between LV basal strain and LA reservoir strain in the non-CA group. Third, the number of patients with CA ($n=75$) was not sufficient to perform multivariate Cox regression analyses for the prediction of heart failure hospitalization due to the lack of statistical power.

Conclusions

LA reservoir strain was tightly coupled with LV longitudinal strain in the cardiac base, especially in patients with CA etiology, and provided the diagnostic ability to discriminate CA from other LVH etiologies. The assessment of LA strain might facilitate the etiological workup of patients with pathological LVH.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12947-025-00339-1.

Supplementary Material 1

Supplementary Material 2

Author contributions

Dr. Inoue K, Nakao Y and Saito M have participated in conception and design of the study, in collection of data and data analysis, have been involved in the drafting of the manuscript and have approved the final version. Dr. Kinoshita M, Dr. Higashi H and Dr. Yamaguchi O have been involved in the drafting of the manuscript and has approved the final version.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Ehime University Graduate School of Medicine (approval numbers: 1803003 and 1905015), and it was performed using the opt-out method of our hospital websites.

Competing interests

The authors declare no competing interests.

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